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Mini-Stern Trial: A randomised trial comparing mini-sternotomy to full median sternotomy for aortic valve replacement

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Question	**Response**
Please submit your article's Central Message here. The text box will limit you to 200 characters, spaces included	In the UK NHS, compared to conventional median sternotomy approach for surgical AVR, mini-sternotomy did not hasten recovery or hospital discharge, and was not cost-effective.
Please submit your article's Perspective Statement here. The text box will limit you to 405 characters, spaces included	Minimal access surgery is appealing for its perceived advantages including better patient recovery, satisfaction and cost-effectiveness. This RCT conducted within the UK NHS setting did not demonstrate quicker patient recovery or cost-effectiveness associated with mini-sternotomy compared to full median sternotomy approach. These findings are relevant to physicians, patients and health care funders.
Please submit the abbreviated legend for your Central Picture. The text box will limit you to 90 characters, spaces included	Duration of hospital stay after AVR: FS versus MS.

Mini-Stern Trial: A randomised trial comparing mini-sternotomy to full median sternotomy for aortic valve replacement

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Glossary of Abbreviations

AVR	aortic valve replacement
mAVR	minimal access aortic valve replacement
BMI	body mass index
CI	95% confidence interval
COPD	chronic obstructive pulmonary disease
CPB	cardiopulmonary bypass
FEV_1	forced expiratory volume in one second
FS	full median sternotomy
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
LVEF	left ventricular ejection fraction
MS	mini-sternotomy
NHS	National Health Service
OR	odds ratio
QALY	quality-adjusted life year
RCT	randomised control trial
SAE	serious adverse event
SD	standard deviation
TLCO	transfer factor of the lung for carbon monoxide
TOE	transoesophageal echocardiogram
UK	United Kingdom

Central Message

In the UK NHS, compared to conventional median sternotomy approach for surgical AVR, mini-sternotomy did not hasten recovery or hospital discharge, and was not cost-effective.

Perspective Statement

Minimal access surgery is appealing for its perceived advantages including better patient recovery, satisfaction and cost-effectiveness. This RCT conducted within the UK NHS setting did not demonstrate quicker patient recovery or cost-effectiveness associated with mini-sternotomy compared to full median sternotomy approach. These findings are relevant to physicians, patients and health care funders.

Structured Abstract

Objective: Aortic valve replacement (AVR) can be performed either through full median sternotomy (FS) or upper mini-sternotomy (MS). The Mini-Stern trial aimed to establish whether MS leads to quicker postoperative recovery and shorter hospital stay after first-time isolated AVR.

Methods: This pragmatic, open-label, parallel RCT compared MS with FS for first-time isolated AVR in two UK NHS hospitals. Primary endpoints were duration of postoperative hospital stay and the time to fitness for discharge from hospital after AVR, analysed in the intent-to-treat population.

Results: In this RCT, 222 patients were recruited and randomised (118 MS, 104 FS). Compared to FS patients, MS patients had longer hospital stay (mean 9.5 vs. 8.6 days) and took longer to achieve fitness for discharge home (mean 8.5 vs. 7.5 days). Adjusting for valve type, sex and surgeon, hazard ratios (HR) from Cox models did not show a statistically significant effect of MS (relative to FS) on either hospital stay (HR 0.874, 95% CI 0.668-1.143, p-value 0.3246) or time to fitness for discharge (HR 0.907, 95% CI 0.688-1.197, p-value 0.4914). During mean follow up of 760 days (MS:745 and FS:777 days), 12 (10%) MS and 7 (7%) FS patients died (HR 1.871, 95% CI 0.723-4.844, p-value 0.1966). Average extra cost for MS was £1,714, during the first 12 months after AVR.

Conclusions: Compared to FS for AVR, MS did not result in shorter hospital stay, faster recovery or improved survival and was not cost-effective. MS approach is not superior to FS for performing AVR.

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Introduction

Aortic valve replacement (AVR) is the second commonest cardiac surgery in the UK [1] with an increasing proportion of older patients [1, 2]. Minimal access AVR (mAVR) might shorten hospital stay and postoperative recovery period and could be beneficial if offered safely and cost-effectively.

Currently, most AVRs are performed safely through full median sternotomy (FS) [2-6]. However, mAVR may be associated with less postoperative pain, blood loss, pulmonary and wound complications and shorter hospital stay [2]. The most commonly practised mAVR involves mini-sternotomy (MS), which could potentially hasten postoperative recovery, shorten hospital stay and improve patient satisfaction [2-10].

Most studies comparing MS and FS for AVR are non-randomised. Although systematic reviews with meta-analyses [11, 12] have been conducted, inadequate statistical power and heterogeneity of studies calls for prospective, randomised control trials (RCTs) to assess benefits and risks of mAVR. Published evidence on cost-effectiveness comparing MS to FS is sparse and weak. A recent review comparing cost-effectiveness of FS and MS called for a well-designed RCT to evaluate cost-effectiveness of mAVR up to at least a year after surgery [13]. Recently, a propensity-matched study from the UK national data concluded that mAVR is safe and was associated with shorter postoperative hospital stay [14]. The authors concluded that although general clinical equipoise exists between FS and MS, it is essential to have a well-constructed and adequately powered RCT before widespread adoption of MS. This retrospective study did not analyse cost-effectiveness of either surgical approach.

The Mini-Stern trial assessed whether MS is superior to FS in shortening postoperative recovery time and improving patient outcomes without compromising patient safety. It also assessed cost-effectiveness of MS from the perspective of the UK NHS as a health care provider.

Materials and Methods

Mini-Stern was a two-centre, pragmatic, open-label RCT conducted in the UK. Patients were randomised (1:1) to AVR either by MS or FS.

Sample Size

Considering four published RCTs [5, 6, 9, 10] and two cohort studies [7, 8], a 20% reduction in hospital stay from 11.7 to 9.36 days was considered clinically significant. Based on an internal audit of 252 first-time elective AVRs performed at Papworth Hospital in 2007/08 (mean hospital stay 11.7 days, SD 6.2), to detect this change with 80% power and 2-sided significance of 5%, 110 patients per group were required. As randomisation was performed on the day of surgery after induction of anaesthesia and introduction of the transoesophageal echocardiogram (TOE) probe, no subjects dropped out between randomisation and surgery thereby making the total trial recruitment target, 220 patients.

Recruitment

Adult patients undergoing first-time isolated AVR were included. Exclusion criteria included emergency AVR, LVEF≤ 30%, chest wall deformities, severe COPD (FEV_1 or TLCO < 40% predicted), BMI > 35kg/m^2, concomitant cardiac surgery, redo-surgery and inability to perform TOE. Details of patient enrolment are given in the online protocol.

Randomisation

Randomisation (1:1) used random permuted blocks of variable lengths (6 or 8), stratified by surgeon and valve prosthesis (bio-prosthetic or mechanical). Random allocations were pre-generated, held in secure files by Papworth Trials Unit. During early days of the trial, TOE probe could not be passed in four patients due to technical reasons. These patients underwent the allocated procedure and were included in the trial. Later the Trial Steering Committee decided that under such circumstances, MS would be unsafe and patients should be excluded from the trial to FS. Since eligibility for MS required TOE, in order to avoid post-randomisation drop-out, group allocation for the study subjects was retrieved via telephone by theatre staff soon after anaesthesia and introduction of the TOE probe. Due to the nature of interventions, this trial could not be blinded.

Outcomes

Primary endpoints: Two closely related primary endpoints were measured. Firstly, length of postoperative hospital stay (days between surgery and actual hospital discharge) which is easily measured, a surrogate for early postoperative events and sensitive to outcomes that affect health-related quality of life (HRQoL). Secondly, the interval in days between surgery and the patient being medically fit for discharge. To reduce investigator bias, standard discharge criteria were followed to decide the day of fitness for discharge. This endpoint was chosen to address exogenous effects (social factors, lack of transport, non-availability of space in nursing homes etc.) that commonly delay hospital discharge in the UK.

Clinical secondary endpoints: duration of surgery, total theatre time, aortic cross-clamp and cardiopulmonary bypass (CPB) times, blood loss in the first 12 hours after surgery, transfusion of blood and clotting products in the first 48 hours (blood transfusion trigger was

haemoglobin level < 80g/L), frequency of re-intubation, time to initial extubation, mediastinal drain removal and first independent mobilisation, daily pain scores at rest and on deep breath (over the first ten days or until hospital discharge) on a scale of 0 to 10, LVEF and severity of para-prosthetic regurgitation at hospital discharge and at 6 months, and time to all-cause death. Definitions of adverse events and details of their reporting are in the online protocol. To exclude bias, clinical outcome data were collected by research team who were not involved in routine care of subjects, following standardised protocols.

Non-clinical secondary endpoints: Health-related Quality of Life and Healthcare resource use.

HRQoL: Patients completed EQ-5D-3L [15] and SF-36 [16, 17] questionnaires at baseline, 6 weeks, 6 months and 12 months following surgery. EQ-5D-3L was repeated on fourth postoperative day and at discharge.

Healthcare resource use: Patient-specific resource use collected from hospital records and patient interviews during the primary admission included phases of care including operative surgery, critical care, post-surgical ward care and medications. Post-discharge resource use included attending wound clinics, community nurse visits, physiotherapy sessions, occupational therapy services, medical tests, cost of analgesics and other drugs and further hospitalisation within the first year after AVR.

Surgical details

All participating surgeons were consultants experienced in performing AVR by both FS and MS. They followed the operative surgical protocol as described below.

MS approach: With the patient anaesthetised as per standard protocol, skin was incised from half-way between the suprasternal notch and the sternal angle to the level of the fourth

intercostal space, measuring approximately 8cm. The manubrium was divided in the midline from the suprasternal notch inferiorly and then into the right 4th intercostal space. Thymus was divided and pericardium opened exposing the ascending aorta, aortic root and right atrial appendage. A loading dose of unfractionated heparin 300U/kg followed by boluses of 5000U was administered to achieve activated clotting time above 450 seconds. Aorta was cannulated using a wired flexible aortic cannula. Right atrial appendage was cannulated using a flat venous cannula and CPB commenced. The ascending aorta was cross-clamped and intermittent, antegrade, cold blood cardioplegia administered. The aorta was then incised open in an oblique or transverse fashion, the diseased valve excised and annulus decalcified. A suitably sized aortic valve prosthesis was inserted using either horizontal mattress, 2-0 Ethibond sutures or semi-continuous, 2-0 Prolene sutures. Surgeons adopted either of these suture techniques and adhered to the same technique irrespective of the type of valve prosthesis or the surgical approach. Aortotomy was then closed, heart de-aired, right atrial and ventricular epicardial pacing wires inserted and patient weaned off CPB. After confirming satisfactory functioning of the aortic valve prosthesis by TOE, heparin was reversed with protamine (1mg/100U of heparin). Chest drains were inserted into the anterior mediastinum, posterior pericardial space and pleural space if necessary. Sternal wires were inserted and incision closed in layers. Conversion to FS was performed to ensure patient safety if access was difficult or if intraoperative complications occurred.

FS approach: Anaesthesia and positioning of patients was the same as for MS approach. The skin incision was made between the suprasternal notch and the xiphoid process and sternum divided in the midline from the suprasternal notch to the xiphoid process. A two-stage venous cannula was used for atrial cannulation. Remaining steps were similar to MS approach.

Statistical analysis

Analyses of primary and secondary endpoints used intention-to-treat and included all randomised patients. Unless stated otherwise, statistical models included treatment (MS vs. FS), valve (mechanical vs. bio-prosthetic) and sex as fixed effects, and surgeons as random effects. Hypothesis testing was two-sided at the 5% significance level, with no adjustments for multiple testing. All confidence intervals (CI) were estimated at the 95% confidence level.

Distributions of time-to-event endpoints were compared between study groups using Kaplan-Meier curves and log-rank tests (stratified by sex, valve and surgeon). Hazard ratios (HR) for MS relative to FS were estimated from a Cox model. The null hypothesis of no treatment effect (HR = 1) was tested. Patients who were lost to follow-up, withdrew or died before the event were censored at the latest time they were known to be event-free. Models were checked by plotting Schoenfeld and deviance residuals. For primary endpoints, Cox models were re-fitted using the per-protocol population and in sensitivity analyses (Appendix A. Table A4).

Need for reintubation and other dichotomous endpoints were compared between groups by estimating a MS/FS odds ratio (OR) via logistic regression. EQ-5D, SF-36 and pain scores were modelled using repeated measures linear regression. Where possible, random intercepts and random time coefficients for patients were included. For EQ-5D and SF-36, fixed effects for baseline scores were included. Models were fitted using complete cases, then re-fitted with multiple imputation of missing scores via chained equations.

Serious adverse events (SAEs) were analysed in the safety population according to intervention received. Patients randomised to MS who crossed over to FS prior to surgery were considered to have received FS; those who crossed over after MS had commenced were

considered to have received MS. Rates of SAEs were explored using Poisson regression with a random patient effect.

CONSORT guidelines [18] were followed. Analyses were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). No interim analyses were undertaken but reports were presented annually to the Data Monitoring and Ethics Committee.

Economic analysis

Unit costs were obtained from nationally published sources in the UK [19, 20, 21, 22] or from the Finance department, Papworth Hospital when the former did not provide the required information. Total cost per patient was calculated by summing resource use items multiplied by unit costs across the in-patient stay and the 12-month postoperative follow-up period (Appendix B. Table B7). Health state utilities from the EQ-5D-3L and SF-36, based on UK value sets [15, 23] were used to generate quality-adjusted life years (QALYs) using the area under the curve method and assigning a value of zero from date of death. Missing values were imputed using chained predictive mean matching, stratified by treatment and conditional on age, sex and baseline EQ-5D-3L.

Differences in mean costs and QALYs were estimated using seemingly unrelated regression, controlling for age, sex, valve, baseline EQ-5D-3L and treatment, to accommodate skewness [24]. Uncertainty in cost-effectiveness was estimated by drawing 1000 bootstrapped samples and conducting probabilistic sensitivity analysis. Results are presented as incremental net monetary benefit at various thresholds of willingness to pay per QALY, cost-effectiveness planes and cost-effectiveness acceptability curves. Deterministic sensitivity analyses explored effects of using complete cases only, SF6D-based QALY estimates, the procedure inpatient

admission only, excluding patients who died and excluding additional equipment costs (Appendix B. Table B11).

Results

Overall 1024 patients were screened between 28 January 2010 and 13 April 2015, of whom 222 were recruited and randomised to MS (118) or FS (104). One-year follow-up was completed on 23 May 2016.

Study groups were similar at baseline except for a non-significant sex imbalance (Table 1). In this trial, MS was not completed in 14 (12%) of 118 patients randomised to MS. Of these patients, 6 (5%) had conversion from MS to FS due to reasons listed in Figure 1. The remaining 8 patients underwent FS after randomisation to MS but without initial MS incision as MS was considered unsafe/impractical. The true rate of intraoperative conversion of MS to FS was therefore 5%. Four patients (2%, Table 2) were censored before discharge: one withdrawal before surgery (FS) and three deaths (all randomised to and received MS). A further thirteen (6%) were censored before fitness for discharge: six discharged to acute hospital (three MS, three FS), seven to long-term care or rehabilitation (three FS, four MS).

Mean time to hospital discharge was longer for MS than FS (9.5 vs. 8.6 days), as was mean time to fitness to discharge (8.5 vs. 7.5 days). However, distributions of these endpoints were similar in both groups (Figure 2, Table 2). The difference was not statistically significant in either primary analyses using Cox models (Figure 3), log-rank tests (Table 2) or sensitivity analyses (Appendix A. Table A4). The gamma-distributed frailty term in the Cox models was estimated to have variance 0.006675 for time to fitness and 0.000100 for time to discharge, suggesting that surgeon heterogeneity was negligible.

Time to drain removal (including drains inserted/retained to treat complications) was longer for MS, but times to extubation and independent mobilisation did not differ significantly between groups (Table 2, Figure 3), nor did numbers of patients re-intubated (six MS vs. five FS, OR 1.039, CI 0.306-3.531, p=0.9512). Statistically significant HRs indicated longer surgery, CPB, cross-clamp and theatre times for MS (Figure 3). No significant differences were seen in blood loss (Appendix A. Table A3), or in numbers of patients requiring transfusion of blood (50 MS vs. 51 FS, OR 0.797, CI 0.453-1.402, p=0.4310) or clotting products (11 MS vs 4 FS, OR 2.616, CI 0.801-8.541, p=0.1112).

Regression models for pain at rest, EQ-5D utilities and SF-36 domain scores (Appendix A. Tables A6, A7, A8) estimated greater rate of improvement over time in MS patients for three SF-36 domains (social functioning, vitality and role physical). After multiple imputation, the difference was only significant for the role physical domain (Appendix A. Table A9). Pain on deep breath was not analysed as only less than half the data were collected due to poor patient compliance.

Nine (4%) patients died within a year of surgery: seven (6%) MS, two (2%) FS. Five deaths were possibly related to treatment (four MS, one FS), none were probably or definitely related (Appendix A. Table A15). Overall, twelve (10%) MS and seven (7%) FS patients died during follow-up (mean follow-up 760 days: 745 MS, 777 FS). Time to all-cause death, adjusted for age, showed a moderately large but statistically non-significant HR (MS/FS) of 1.871 (CI 0.723-4.844, p=0.1966).

Safety analyses excluded one patient who was withdrawn before surgery. There were significantly more SAEs in MS recipients (rate ratio 1.615, CI 1.070-2.437, p=0.0225) (Appendix A. Table A11). The numbers of patients experiencing SAEs were not significantly different (OR 1.559, CI 0.895-2.715, p=0.1161). Incidence of para-prosthetic

regurgitation did not differ significantly between groups (Appendix A. Table A13). Seven patients developed pericardial collection (three MS vs four FS, OR 0.680, CI 0.146-3.178, p=0.6229). Wound infections (including superficial and deep infections) were more common in FS recipients (thirteen FS vs four MS, OR 0.312, CI 0.097-1.005, p=0.0511). Deep sternal wound infection developed in one MS and one FS recipient, neither of whom required plastic surgical repair.

Economic analyses are summarised in Table 4. There was additional cost for MS relative to FS (£1,714 per patient, p=0.0765) in the first year following surgery. MS patients had (non-significant) better EQ-5D-based QALYs (0.03 per patient, p=0.1509). The incremental cost per QALY gained was £61,379, but after adjusting for baseline characteristics, MS had higher costs and lower QALYs (i.e. was dominated). In deterministic and probabilistic sensitivity analyses, MS was either dominated or had a very large cost per QALY, except for the complete case analysis (Appendix B. Tables B11, B12).

Discussion

The UK NHS is a free for patient at point-of-delivery healthcare system. Apart from good recovery, hospital discharge of a significant proportion of elderly patients depends on the timely availability of social care services in the community. The Mini-Stern trial is the first RCT comparing FS and MS for isolated AVR when performed for UK NHS patients.

In this prospective, pragmatic, open-label RCT, MS did not reduce the total duration of hospital stay after AVR. As hospital discharge is sometimes delayed due to social factors, we included time until fit for discharge as a second primary endpoint. This was also not reduced by MS. These endpoints were recorded by physiotherapists based on a common discharge

protocol with specific clinical milestones to achieve, thereby excluding physician-induced bias.

In this study operation, total theatre, aortic cross-clamp and CPB times were significantly prolonged with MS. This was expected as in general, minimal access valve operations take longer [5, 9]. This is justifiable if MS resulted in either faster recovery, shorter postoperative stay, reduced cost of treatment or more importantly a significant reduction in adverse events and therefore superior patient safety. In this RCT, MS did not achieve these benefits and hence we feel that the prolonged operation time, total theatre, cross-clamp and CPB times are not justifiable for performing AVR through MS.

Previously, two meta-analyses [11, 12] concluded that mAVR approaches are superior in certain aspects of postoperative recovery. However, both included studies on mini-thoracotomy approach for AVR, and therefore inferences drawn cannot be extrapolated to MS. A retrospective propensity-matched analysis of data from a UK national database concluded that MS is safe and comparable to conventional AVR [14]. The authors found that MS resulted in a shorter postoperative hospital stay, which disagrees with our findings. However, a propensity-matched study can suffer from selection bias if its matching algorithm produces treatment groups that are unbalanced in some unobserved characteristics. Recently, a retrospective study demonstrated safety of right thoracotomy minimally invasive isolated and concomitant AVR in patients of all age groups [25]. As randomisation balances study groups in known and unknown characteristics, results of the Mini-Stern trial should be more reliable than non-randomised studies.

Previous studies investigating cost-effectiveness provided unclear answers. A report analysing registry data from patients who underwent isolated primary AVR [26] reported lower hospital cost when AVR was performed through right anterior thoracotomy compared to sternotomy-based approaches with no significant differences in outcome. The main reasons attributed to lower costs were earlier hospital discharge and reduced use of blood products. Ghanta et al [27] noted that exclusion of rehabilitation costs could alter this finding. A review by Glauber et al [13], based on uncontrolled studies, noted that higher cost of instruments and devices in mAVR could be offset by economic advantage gained by shorter hospital stay and lower complication rates. The Mini-Stern trial assessed cost-effectiveness using a range of sensitivity analyses, but only the complete case analysis showed MS to be cost-effective, suggesting lower costs but slightly worse outcomes with MS. However, this analysis used a potentially unrepresentative sample of just 90 patients. Our analysis was restricted to the first year following operation without long-term analysis beyond 1 year.

This RCT is robust with many merits including on-table randomisation, comprehensive and independent outcome assessment without physician-bias, longer-term clinical assessment, HRQoL analysis and economic analysis. However there were some limitations. Although we report on secondary endpoints, this trial was powered only to address the primary endpoint. A total of 14 patients (12%) allocated to MS received FS, which could be another limitation. However, only 6 patients (5%) had true conversion after an attempted MS, while 8 patients (6.7%) went on to FS for safety reasons. Although this RCT took place in only two centres, thereby limiting generalisability, recruitment by eight surgeons improves generalisability. A total of 1024 patients were screened to recruit 222 (21.7%) patients. Although this potentially suggests selection bias, only 125 eligible patients (12.2%) failed recruitment while the remaining 667 patients (65.1%) did not meet inclusion criteria. Blinding was not

practical as sternotomy dressings were usually changed 48 hours after surgery and patients became aware of the approach. This could have caused bias in self-reported outcomes. Missing 'pain at rest' data were unlikely to be missing at random, and therefore imputation might not have addressed all potential biases. Despite having two primary outcomes, we did not adjust for multiple testing. However, as neither showed a significant difference between groups, this would not have affected our conclusions.

In conclusion, MS for AVR did not result in quicker recovery or earlier hospital discharge. MS resulted in longer operations, increased costs, and resulted in more SAEs than FS. Overall, this pragmatic RCT did not provide evidence that MS results in better clinical or quality of life outcomes, or that MS is cost-effective compared to FS in the first year after AVR.

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Legends

Central Picture Legend: Duration of hospital stay after AVR: FS versus MS.

Video Legend: MS approach for AVR.

Figure 1. Trial flow diagram.

Figure 2. Kaplan-Meier curves for primary endpoints. Points indicate censoring and dashed lines represent 95% confidence intervals.

Figure 3. Forest plot of HRs and 95% confidence intervals from Cox models.

Figure 4. Cost-effectiveness planes. Proportion of points below each threshold gives the probability that MS is more cost-effective than FS. This probability is 3.7% for willingness to pay £20,000/QALY and 5.1% for willingness to pay £30,000/QALY.

412 **Table 1. Baseline characteristics**

	MS (n = 118)	**FS (n = 104)**
Age (years) - Mean (SD)	71.3 (12.3)	72.1 (10.9)
BMI (kg/m^2) – Mean (SD)	26.6 (3.2)	27.7 (3.7)
Sex - frequency (%)		
Female	53 (45%)	57 (55%)
Male	65 (55%)	47 (45%)
Valve type - frequency (%)		
Mechanical	15 (13%)	14 (13%)
Tissue	103 (87%)	90 (87%)
EuroSCORE (%) - Mean (SD)	5.9 (2.1) *	6.1 (2.1)

413 * EuroSCORE was missing for one MS patient.

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417 **Table 2. Kaplan-Meier medians (quartiles) for time-to-event endpoints**

	MS (n = 118)	FS (n = 104)	p-value*
Time to discharge (days)	7 (6, 10)	7 (6, 10)	0.6924
Censored	3	1	
Time until fit for discharge (days)	6 (5, 10)	6 (5, 9)	0.5597
Censored	10	7	
Time to independent mobilisation (days)	4 (3, 7)	4 (3, 6)	0.5819
Censored	8	7	
Time to mediastinal drain removal (hours)	26.1 (20.6, 53.3)	22.5 (19.4, 37.8)	0.0157
Censored	2	2	
Time to extubation (hours)	9.2 (7.8, 12.1)	8.3 (6.8, 11.7)	0.5488
Censored	1	1	
Theatre time (minutes)	191 (172, 225)	176 (152, 203)	< 0.0001
Censored	0	0	
CPB time (minutes)	80 (70, 95)	66 (52, 85)	< 0.0001
Censored	0	0	
Cross-clamp time (minutes)	65 (53, 76)	49 (39, 64)	< 0.0001
Censored	0	0	
Surgery duration (minutes)	163 (139, 190)	149 (114, 167)	< 0.0001
Censored	3	4	

418 **Log-rank test. Seven surgery durations were not recorded and censored at 1 minute.*

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420 **Table 3. Costs, QALYs and Cost-effectiveness**

	Cost and QALYs (with imputation)	**FS (n = 118)**		**MS (n = 104)**	
		Mean Cost per patient	**SD**	**Mean Cost per patient**	**SD**
Primary Admission Costs	Theatre use	£3,824	£1,243	£4,422	£2,053
	Additional surgical items	£16.52	£0.0	£52.0	£0.0
	Critical care (ITU)	£1,834	£3,023	£2,934	£5,030
	Cardiac ward	£2,744	£1,664	£2,676	£1,500
	Physio- and Occupational Therapy	£77	£55	£78	£68
	Rehabilitation	£384	£1,878	£263	£1,621
	Acute hospital	£347	£1,919	£298	£1,971
	Sub-total cost	*£9,226*	*£6,511*	*£10,724*	*£8,850*
Post primary admission costs to 12 months	Hospital Re-admission	£418	£1,475	£575	£1,863
	Follow up tests	£224	£258	£282	£279
	Follow up healthcare visits	£373	£359	£311	£263
	Sub-total cost	*£1,015*	*£1,778*	*£1,168*	*£2,079*
	Drugs	£379	£548	£441	£977
	Total cost over 12 months	*£10,620*	*£7,624*	*£12,333*	*£9,864*
Incremental cost-effectiveness* (probabilistic analysis with	Incremental cost at 12 months (MS-FS)			£2,154.0 (*SE* £36)	
	Incremental EQ-5D-3L QALYs (MS-FS)			-0.0122 (SE 0.0008)	
	ICER			MS dominated by FS	
	NMB (at WTP £20,000/QALY)			-£2,397	
	NMB (at WTP £30,000/QALY)			-£2,519	

baseline adjustment)
SD: standard deviation, SE: standard error, WTP: willingness to pay, NMB: net monetary benefit, ICER: incremental cost-effectiveness ratio. * Incremental costs and effects estimated using SUR, adjusting for baseline differences.

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Figure 1

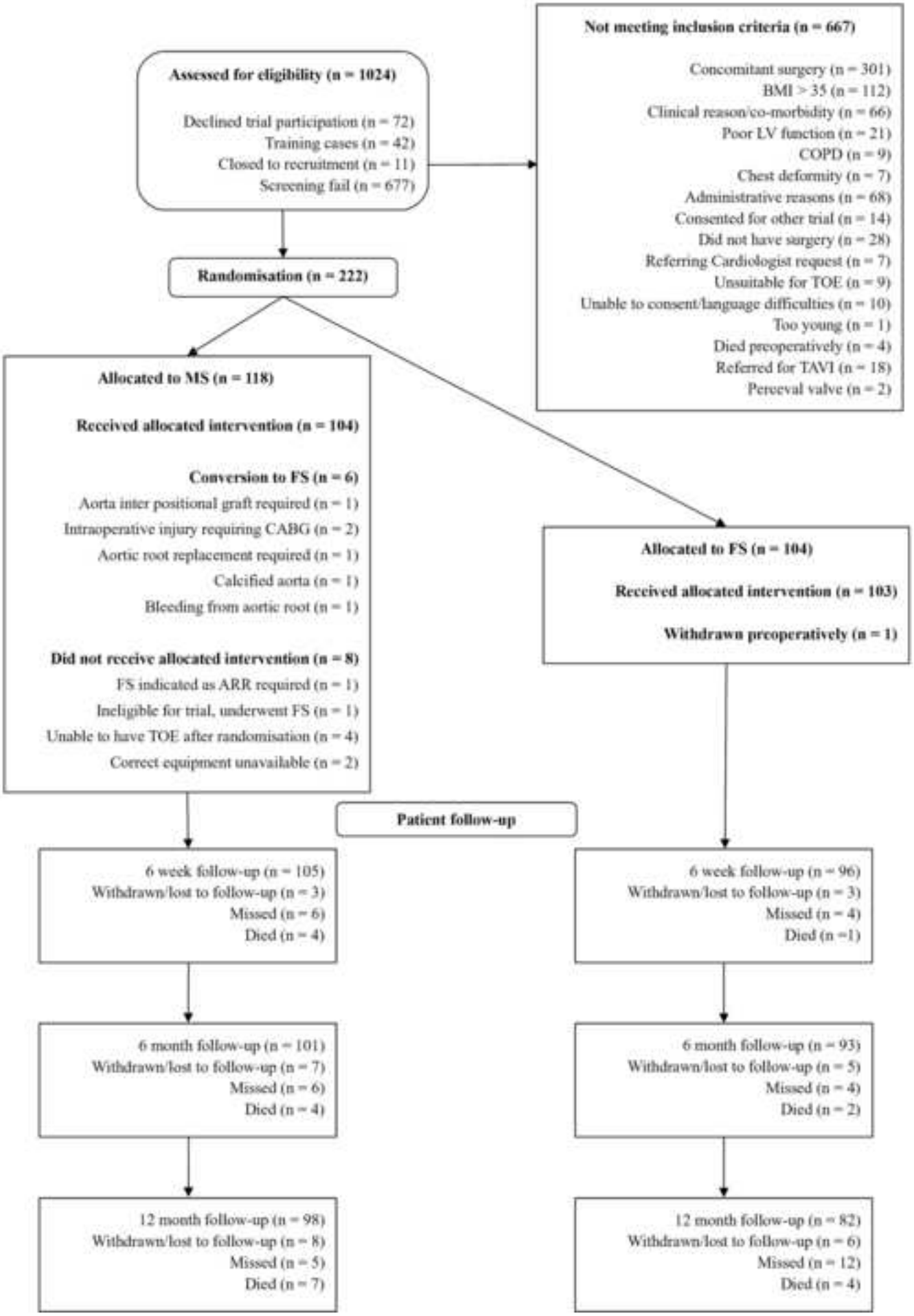

Figure 2

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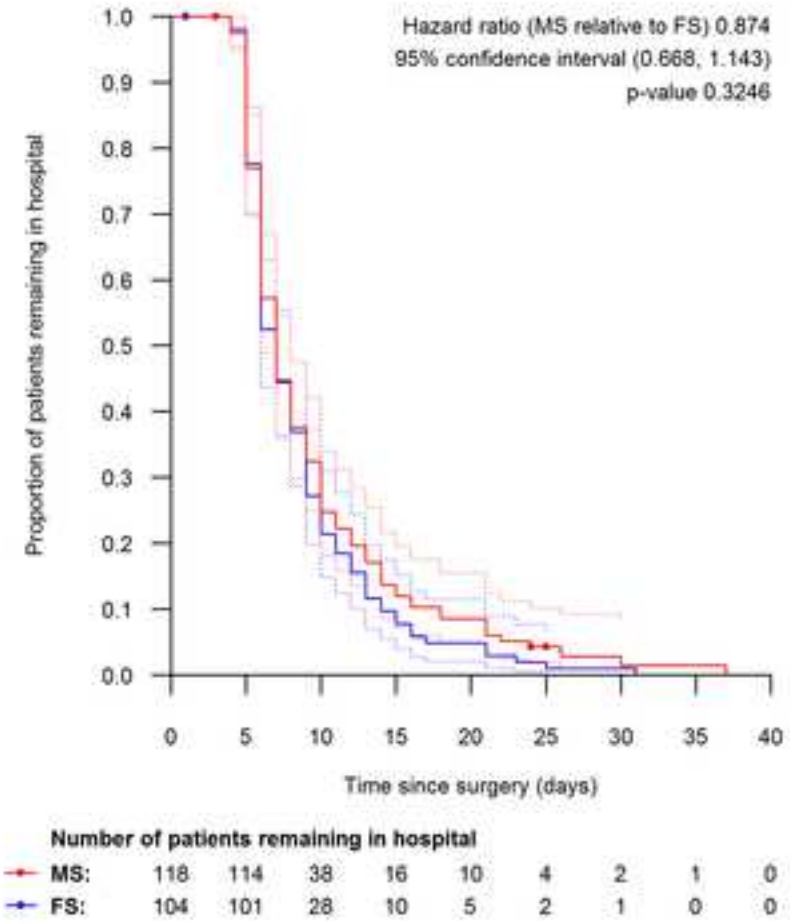

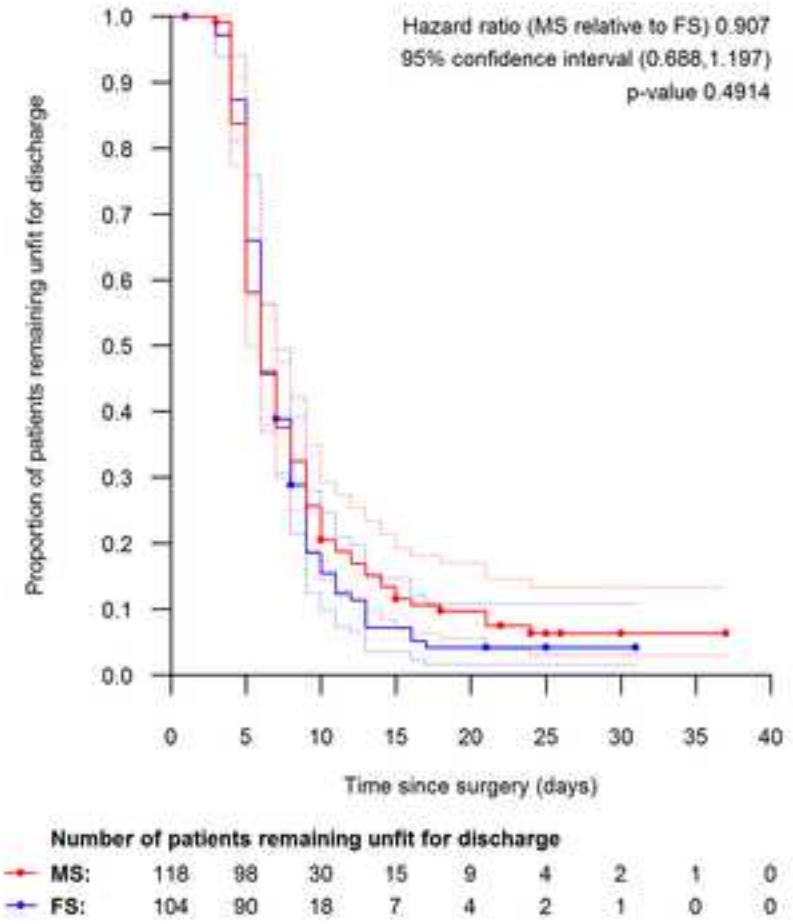

Figure 3

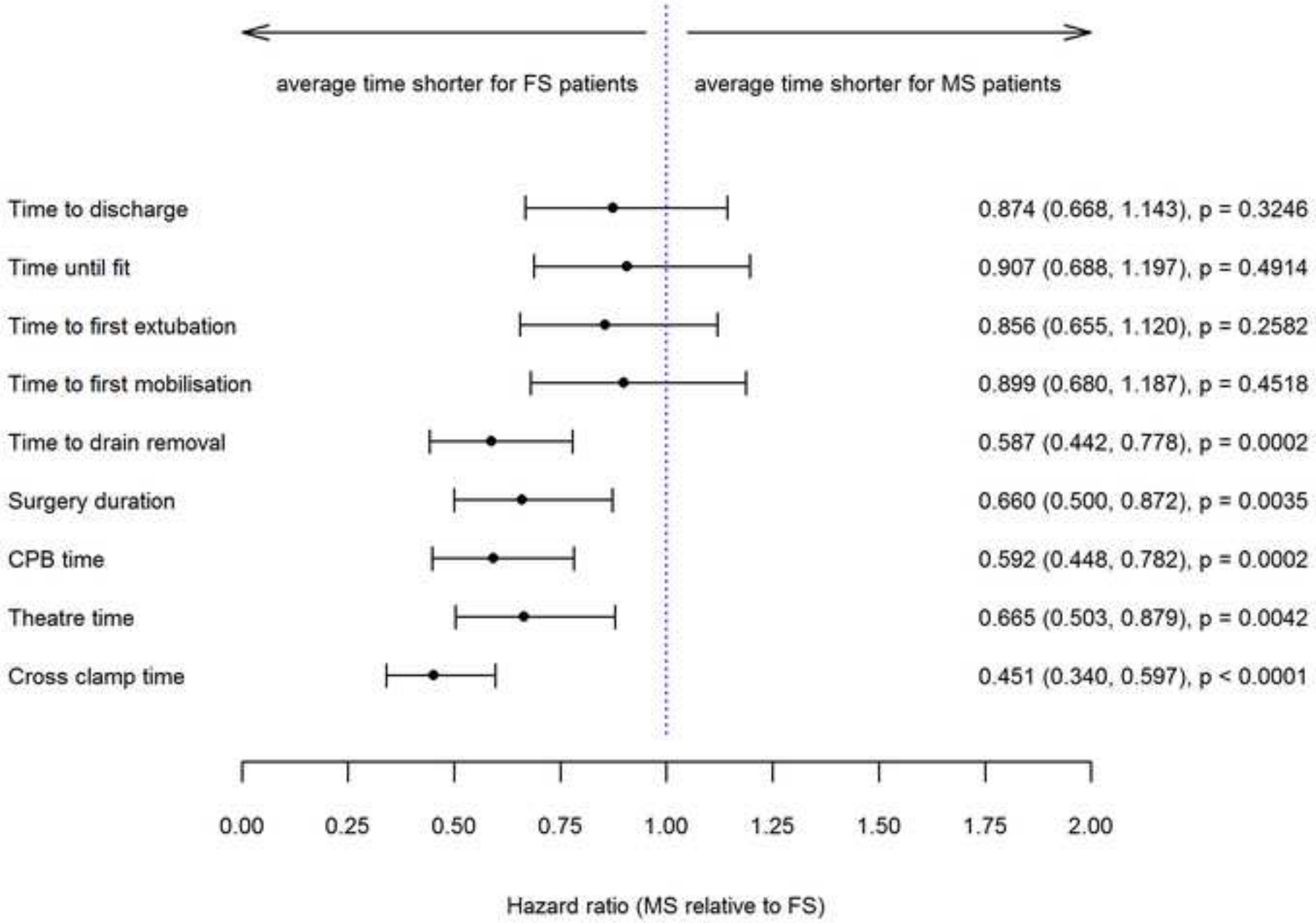

Figure 4

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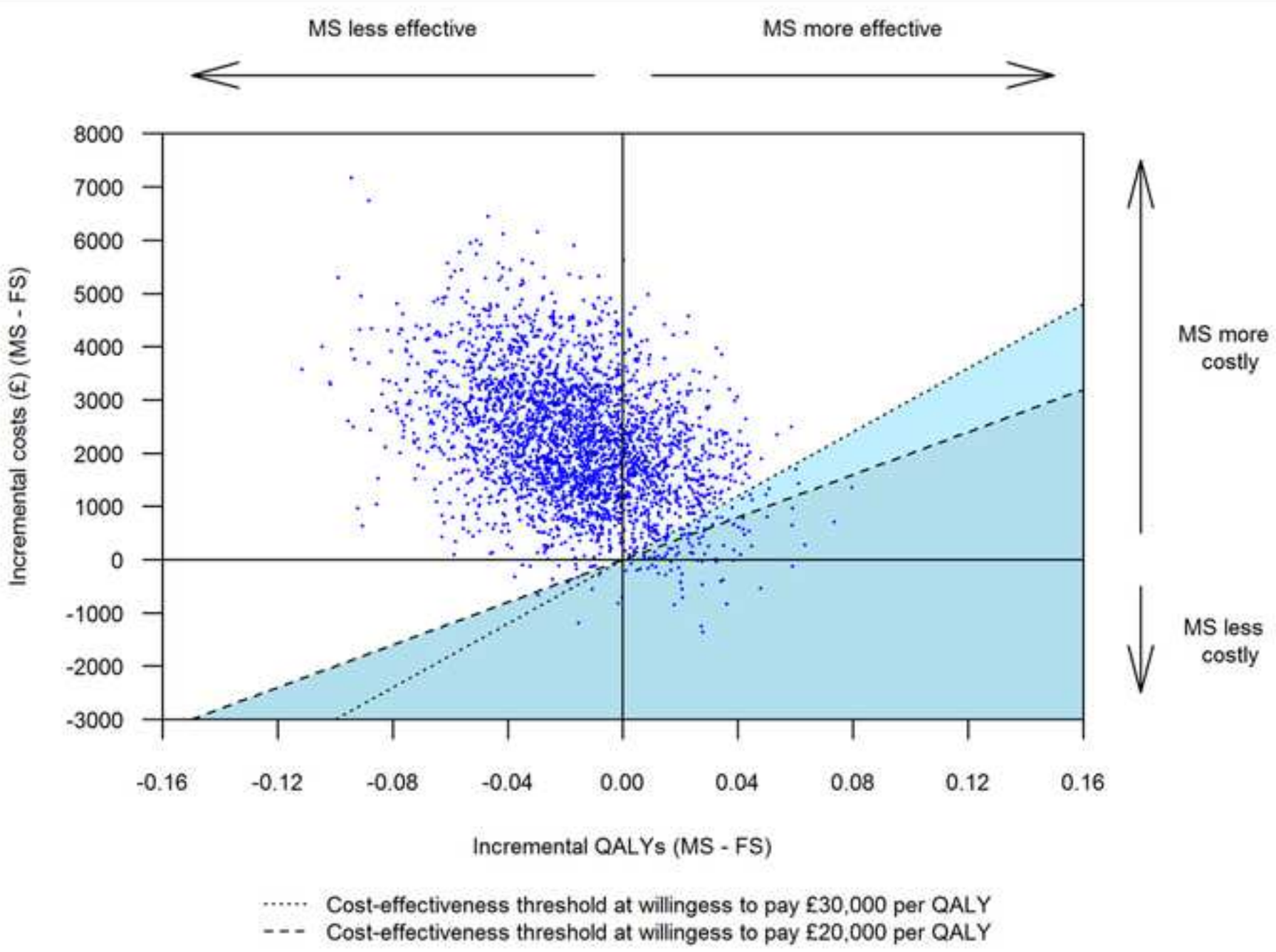

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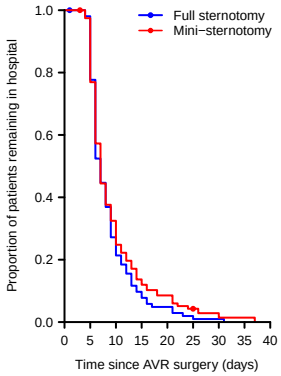

Mini-Stern Trial: A randomised trial comparing mini-sternotomy to full median sternotomy for aortic valve replacement

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~~**Justification for more than 7 authors:** This study was conducted in two surgical units in the UK involving 8 Surgeons, 1 Anaesthetist/Intensivist, 2 Health Economists, 2 Trial Managers and 2 Biostatisticians. Each co-author listed above have contributed significantly to the co-ordination and management of the trial, data collection, data analysis and preparation of the manuscript and hence included in the list of authors. A detailed author contribution form with detailed justification of authorship will be submitted along with the revised manuscript on acceptance for publication.~~

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Glossary of Abbreviations

AVR	aortic valve replacement
mAVR	minimal access aortic valve replacement
BMI	body mass index
CI	95% confidence interval
COPD	chronic obstructive pulmonary disease
CPB	cardiopulmonary bypass
FEV_1	forced expiratory volume in one second
FS	full median sternotomy
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
LVEF	left ventricular ejection fraction
MS	mini-sternotomy
NHS	National Health Service
OR	odds ratio
QALY	quality-adjusted life year
RCT	randomised control trial
SAE	serious adverse event
SD	standard deviation
TLCO	transfer factor of the lung for carbon monoxide
TOE	transoesophageal echocardiogram
UK	United Kingdom

Central Message

In the UK NHS, compared to conventional median sternotomy approach for surgical AVR, mini-sternotomy did not hasten recovery or hospital discharge, and was not cost-effective.

Perspective Statement

Minimal access surgery is appealing for its perceived advantages including better patient recovery, satisfaction and cost-effectiveness. This RCT conducted within the UK NHS setting did not demonstrate quicker patient recovery or cost-effectiveness associated with mini-sternotomy compared to full median sternotomy approach. These findings are relevant to physicians, patients and health care funders.

Structured Abstract

Objective: Aortic valve replacement (AVR) can be performed either through full median sternotomy (FS) or upper mini-sternotomy (MS). The Mini-Stern trial aimed to establish whether MS leads to quicker postoperative recovery and shorter ~~postoperative~~ hospital stay after first-time isolated AVR.

Methods: This pragmatic, open-label, parallel RCT compared MS with FS for first-time isolated AVR ~~patients~~ in two UK NHS hospitals. Primary endpoints were duration of postoperative hospital stay and the time to fitness for discharge from hospital after AVR, analysed in the intent-to-treat population.

Results: In this RCT, 222 patients were recruited and randomised (118 MS, 104 FS). Compared to FS patients, MS patients had longer hospital stay (mean 9.5 vs. 8.6 days) and took longer to achieve fitness for discharge home (mean 8.5 vs. 7.5 days). Adjusting for valve type, sex and surgeon, hazard ratios (HR) from Cox models did not show a statistically significant effect of MS (relative to FS) on either hospital stay (HR 0.874, 95% CI 0.668-1.143, p-value 0.3246) or time to fitness for discharge ~~home~~ (HR 0.907, 95% CI 0.688-1.197, p-value 0.4914). During mean follow up of 760 days (MS:745 and FS:777 days), ~~follow-up,~~ 12 (10%) MS and 7 (7%) FS patients died (HR 1.871, 95% CI 0.723-4.844, p-value 0.1966). Average extra cost for MS was £1,714, ~~patients had higher cost of treatment~~ during the first 12 months after AVR.

Conclusions: Compared to FS ~~approach for~~ for AVR, MS did not result in shorter hospital stay, faster recovery or improved survival and was not cost-effective. MS approach is not superior to FS for performing AVR.

Word count for Abstract: ~~242~~248

Introduction

Aortic valve replacement (AVR) is the second commonest ~~adult~~ cardiac surgery in the UK [1] with an increasing proportion of older patients [1, 2]. Minimal access AVR (mAVR) might shorten hospital stay and ~~,~~ postoperative recovery period and could be beneficial if offered cost-effectively without compromising safety~~quality of care~~.

Currently, most AVRs are performed safely through~~via~~ full median sternotomy (FS) [2-6]. ~~which allows safe conduct of the operation. The disadvantages include a longer incision and full-length sternotomy, which might prolong recovery.~~ However, ~~Although results vary among centres,~~ mAVR~~inimally invasive approach~~ may be ~~is~~ associated with less postoperative pain, blood loss, pulmonary and wound complications and shorter hospital stay [2]. The most commonly practised mAVR involves mini-sternotomy (MS) ~~incision~~, which could potentially hasten postoperative recovery, shorten ~~reducing~~ hospital stay and improv~~eing~~ patient satisfaction [2-10].

Most ~~The majority of~~ studies ~~publications~~ comparing MS and FS for AVR are~~represent~~ non-randomised. ~~studies.~~ Although systematic reviews with meta-analyses [11, 12] have been conducted, inadequate statistical power and heterogeneity of studies calls for~~reinforced the need for~~ prospective, randomised control trials (RCTs) to assess benefits and risks of mAVR. Published evidence on cost-effectiveness comparing ~~of~~ MS ~~compared~~ to FS ~~approach~~ is ~~also~~ sparse and weak. A recent review comparing cost-effectiveness of FS and MS called for a well-designed RCT to evaluate cost-effectiveness of mAVR up to at least a year after surgery [13]. Recently a propensity-matched study from the UK national data concluded that mAVR is safe and was associated with ~~a~~ shorter postoperative hospital stay [14]. The authors concluded that although general ~~there is general~~ clinical equipoise exists between FS and MS

approach, it is essential to have a well-constructed and adequately powered prospective RCT before widespread adoption of MS. approach. This retrospective study did not analyse cost-effectiveness of either surgical approach.

The Mini-Stern trial assessed was designed to assess whether MS is superior to FS in shortening postoperative recovery time and improving patient outcomes without compromising patient safety. It also assessed cost-effectiveness of MS approach from the perspective of the UK NHS as a health care provider.

Materials and Methods

Mini-Stern was a two-centre, pragmatic, open-label RCT conducted in the UK. Patients were randomised (1:1) to AVR either by a MS or FS approach.

Sample Size

Considering four published RCTs [5, 6, 9, 10] and two cohort studies [7, 8], a 20% reduction in hospital stay from 11.7 to 9.36 days was considered clinically significant. Based on an internal audit of 252 first-time elective AVRs performed at Papworth Hospital in 2007/08 (mean hospital stay 11.7 days, SDstandard deviation 6.2), to detect this change with 80% power and a 2-sided significance of 5%, 110 patients per group were required. As randomisation was performed on the day of surgery after induction of anaesthesia and introduction of the transoesophageal echocardiogram (TOE) probe, no subjects dropped out

between randomisation and surgery thereby making the total trial recruitment target, 220 patients.

Recruitment

Adult patients undergoing first-time isolated AVR were included. Exclusion criteria included emergency AVR~~operations~~, LVEF≤ 30%, chest wall deformities, severe ~~emphysema or~~ COPD (FEV_1 or TLCO < 40% predicted), BMI > 35kg/m^2, concomitant cardiac surgery, redo-surgery and inability to perform TOE. Details of patient enrolment are given in the online protocol.

Randomisation

Randomisation (1:1) used random permuted blocks of variable lengths (6 or 8), stratified by surgeon and valve prosthesis (bio-prosthetic or mechanical). Random allocations were pre-generated, held in secure files by Papworth Trials Unit. During early days of the trial, TOE probe could not be passed in four patients due to technical reasons. These patients underwent the allocated procedure and were included in the trial. Later the Trial Steering Committee decided that under such circumstances, MS would be unsafe and patients should be excluded from the trial to FS. Since eligibility for MS required ~~a~~ TOE, in order to avoid post-randomisation drop-out, group allocation for the study subjects was retrieved via telephone by theatre staff soon after anaesthesia and introduction of the TOE probe. Due to the nature of ~~the~~ interventions, thise trial could not be blinded.

Outcomes

Primary endpoints: Two closely related primary endpoints were measured. Firstly, length of postoperative hospital stay (days between surgery and actual hospital discharge) which is easily measured, a surrogate for early postoperative events and sensitive to outcomes that affect health-related quality of life (HRQoL). Secondly, the interval in days between surgery and the patient being ~~considered~~ medically fit for discharge. To ~~In order to~~ reduce investigator bias, standard discharge criteria were followed to decide the day of fitness for discharge. This endpoint was chosen to address exogenous effects (social factors, lack of transport, non-availability of space in nursing homes etc.) that commonly delay hospital discharge ~~of patients~~ in the UK.

Clinical secondary endpoints: duration of surgery, total theatre time, aortic cross-clamp and cardiopulmonary bypass (CPB) times, blood loss in the first 12 hours after surgery, transfusion of blood and clotting products in the first 48 hours (blood transfusion trigger was haemoglobin level < 80g/L), frequency of re-intubation, time to initial extubation, mediastinal drain removal and first independent mobilisation ~~(walking unassisted or with mobility aid if required)~~, daily pain scores at rest and on deep breath (over the first ten days or until hospital discharge) on a scale of 0 to 10, LVEF and severity of para-prosthetic regurgitation ~~(assessed by echocardiography~~ at hospital discharge and at 6 months~~)~~, and time to all-cause death. Definitions of adverse events and details of their reporting are ~~given~~ in the online protocol. To~~In order to~~ exclude bias, clinical outcome data were collected by research team ~~staff~~ who were not involved in routine care of ~~trial~~ subjects, following standardised protocols.

Non-clinical secondary endpoints: Health-related Quality of Life and Healthcare resource use.

HRQoL: Patients completed EQ-5D-3L [15] and SF-36 [16, 17] questionnaires at baseline, 6 weeks, 6 months and 12 months following surgery. EQ-5D-3L was ~~also~~ repeated on~~at~~ fourth postoperative day ~~4~~ and at discharge.

Healthcare resource use: Patient-specific resource use collected from hospital records and patient interviews during the primary admission included ~~various~~ phases of care including operative surgery, ~~post-surgical~~ critical care, ~~care in the~~ post-surgical ward care~~-care~~ and medications. Post-discharge resource use included attending wound clinics, community~~/district~~ nurse visits, physiotherapy sessions, ~~use of~~ occupational therapy services, medical tests, cost of ~~use of~~ analgesic~~s~~a and other drugs ~~and other pharmaceutical expenses,~~ and further hospitalisation ~~admissions~~ within the first year after AVR.

Surgical details

All participating ~~cardiac~~ surgeons were consultants experienced in performing AVR by both FS and MS. They ~~All participating surgeons agreed on and~~ followed ~~adhered to~~ the operative surgical protocol as described below.

MS approach: With the patient anaesthetised as per standard protocol, skin was incised from half-way between the suprasternal notch and the sternal angle to the level of the fourth intercostal space, measuring approximately 8cm. The manubrium was divided in the midline from the suprasternal notch inferiorly and then into the right 4th intercostal space. Thymus was divided ~~in the midline~~ and pericardium opened exposing the ascending aorta, aortic root and right atrial appendage. A loading dose of unfractionated h~~H~~eparin 300U/kg followed by boluses of 5000U was administered to achieve activated clotting time above 450 seconds. Aorta was cannulated using a wired flexible aortic cannula. Right atrial appendage was

cannulated using a flat venous cannula and CPB commenced. The ascending aorta was cross-clamped and intermittent, antegrade, cold blood cardioplegia administered. The aorta was then incised open in an oblique or transverse fashion, the diseased valve excised and annulus decalcified. A suitably sized aortic valve prosthesis was inserted using either horizontal mattress, 2-0 Ethibond sutures or semi-continuous, 2-0 Prolene sutures. Surgeons adopted either of these suture techniques and adhered to the same technique irrespective of the type of valve prosthesis or the surgical approach. Aortotomy was then closed, heart de-aired, right atrial and ventricular epicardial pacing wires inserted and patient weaned off CPB. After confirming satisfactory functioning of the aortic valve prosthesis by TOE, heparin was reversed with protamine (1mg/100U of h~~H~~eparin). Chest drains were inserted into the anterior mediastinum, posterior pericardial space and pleural space if necessary. Sternal wires were inserted and incision closed in layers. Conversion to FS was performed to ensure patient safety if access was difficult or if intraoperative complications occurred.

FS approach: Anaesthesia and positioning of patients was the same as for MS approach. The skin incision was made between the suprasternal notch and the xiphoid process and sternum divided in the midline from the suprasternal notch to the xiphoid process. A two-stage venous cannula was used for atrial cannulation. Remaining steps were similar to MS approach.

Statistical analysis

Analyses of primary and secondary endpoints used intention-to-treat and included all randomised patients. Unless stated otherwise, statistical models included treatment (MS vs. FS), valve (mechanical vs. bio-prosthetic) and sex as fixed effects, and surgeons as random effects. Hypothesis testing was two-sided at the 5% significance level, with no adjustments for multiple testing. All confidence intervals (CI) were estimated at the 95% confidence level.

Distributions of time-to-event endpoints were compared between study groups using Kaplan-Meier curves and log-rank tests (stratified by sex, valve and surgeon). Hazard ratios (HR) for MS relative to FS were estimated from a Cox model. The null hypothesis of no treatment effect (HR = 1) was tested. Patients who were lost to follow-up, withdrew or died before the event were censored at the latest time they were known to be event-free. Models were checked by plotting Schoenfeld and deviance residuals. For primary endpoints, Cox models were re-fitted using the per-protocol population and in sensitivity analyses (Appendix A. Table A4).

Need for reintubation and other dichotomous endpoints were compared between groups by estimating a MS/FS odds ratio (OR) via logistic regression. EQ-5D, SF-36 and pain scores were modelled using repeated measures linear regression. Where possible, random intercepts and random time coefficients for patients were included. For EQ-5D and SF-36, fixed effects for baseline scores were included. Models were fitted using complete cases, then re-fitted with multiple imputation of missing scores via chained equations.

Serious adverse events (SAEs) were analysed in the safety population according to intervention received. Patients randomised to MS who crossed over to FS prior to surgery were considered to have received FS; those who crossed over after MS had commenced were considered to have received MS. Rates of SAEs were explored using Poisson regression with a random patient effect.

CONSORT guidelines [18] were followed. Analyses were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). No interim analyses were undertaken but reports were presented annually to the Data Monitoring and Ethics Committee.

Economic analysis

Unit costs were obtained from nationally published sources in the UK [19, 20, 21, 22] or from the Finance department, Papworth Hospital when the former did not provide the required information. Total cost per patient was calculated by summing resource use items multiplied by unit costs across the in-patient stay and the 12-month postoperative follow-up period (Appendix B. Table B7). Health state utilities from the EQ-5D-3L and SF-36, based on UK value sets [15, 23] were used to generate quality-adjusted life years (QALYs) using the area under the curve method and assigning a value of zero from date of death. Missing values were imputed using chained predictive mean matching, stratified by treatment and conditional on age, sex and baseline EQ-5D-3L.

Differences in mean costs and QALYs were estimated using seemingly unrelated regression, controlling for age, sex, valve, baseline EQ-5D-3L and treatment, to accommodate skewness [24]. Uncertainty in cost-effectiveness was estimated by drawing 1000 bootstrapped samples and conducting probabilistic sensitivity analysis. Results are presented as incremental net monetary benefit at various thresholds of willingness to pay per QALY, cost-effectiveness planes and cost-effectiveness acceptability curves. Deterministic sensitivity analyses explored effects of using complete cases only, SF6D-based QALY estimates, the procedure inpatient admission only, excluding patients who died and excluding additional equipment costs (Appendix B. Table B11).

Results

Overall 1024 patients were screened ~~between two NHS hospitals in the UK~~ between 28 January 2010 and 13 April 2015, of whom 222 were recruited and randomised to MS (118) or FS (104). One-year follow-up was completed on 23 May 2016.

Study groups were similar at baseline except for a non-significant sex imbalance (Table 1). In this trial, MS ~~approach~~ was not completed in 14 (12%) of 118 patients randomised to MS. Of these patients, 6 (5%) had conversion from MS to FS due to reasons listed in Figure 1. The remaining 8 patients underwent FS after randomisation to MS but without initial MS incision as MS ~~approach~~ was considered unsafe ~~/~~ impractical. ~~in this pragmatic trial.~~ The true rate of intraoperative conversion of MS to FS was therefore 5%. Four patients (2%, Table 2) were censored before discharge: one withdrawal before surgery (FS) and three deaths (all randomised to and received MS). A further thirteen (6%) were censored before fitness for discharge: six discharged to acute hospital (three MS, three FS), seven to long-term care or rehabilitation (three FS, four MS).

Mean time to ~~actual~~ hospital discharge was longer for MS than FS (9.5 vs. 8.6 days), as was mean time to ~~achieve~~ fitness to discharge (8.5 vs. 7.5 days). However, distributions of these endpoints were similar in both groups (Figure 2, Table 2). The difference was not statistically significant in either primary analyses using Cox models (Figure 3), log-rank tests (Table 2) or sensitivity analyses (Appendix A. Table A4). The gamma-distributed frailty term in the Cox models was estimated to have variance 0.006675 for time to fitness and 0.000100 for time to discharge, suggesting that surgeon heterogeneity was negligible.

Time to drain removal (including drains inserted/retained to treat complications) was longer for MS, but times to extubation and independent mobilisation did not differ significantly between groups (Table 2, Figure 3), nor did numbers of patients re-intubated (six MS vs. five FS, OR 1.039, CI 0.306-3.531, p=0.9512). Statistically significant HRs indicated longer surgery, CPB, cross-clamp and theatre times for MS (Figure 3). No significant differences were seen in blood loss (Appendix A. Table A3), or in numbers of patients requiring

transfusion of blood (50 MS vs. 51 FS, OR 0.797, CI 0.453-1.402, p=0.4310) or clotting products (11 MS vs 4 FS, OR 2.616, CI 0.801-8.541, p=0.1112).

Regression models for pain at rest, EQ-5D utilities and SF-36 domain scores (Appendix A. Tables A6, A7, A8~~, A9~~) estimated greater rate of improvement over time in MS patients for three SF-36 domains (social functioning, vitality and role physical). After multiple imputation, the difference was only significant for the role physical domain (Appendix A. Table A9). Pain on deep breath was not analysed as only less than half the data were collected due to poor patient compliance.

Nine (4%) patients died within a year of surgery: seven (6%) MS, ~~and~~ two (2%) FS. Five deaths were possibly related to treatment (four MS, one FS), none were probably or definitely related (Appendix A. Table A15).~~.~~ Overall, twelve (10%) MS and seven (7%) FS patients died during follow-up (mean follow-up 760 days: 745 MS, 777 FS). Time ~~. In Cox models, time~~ to all-cause death, adjusted for age, showed a moderately large but statistically non-significant HR (MS/FS) of 1.871 (CI 0.723-4.844, p=0.1966).

Safety analyses excluded one patient who was withdrawn before surgery. There were significantly more SAEs in MS recipients (rate ratio 1.615, CI 1.070-2.437, p=0.0225) (Appendix A. Table A11). ~~-~~The numbers of patients experiencing SAEs were not significantly different (OR 1.559, CI 0.895-2.715, p=0.1161). Incidence of para-prosthetic regurgitation did not differ significantly between groups (Appendix A. Table A13). Seven patients developed pericardial collection (three MS vs four FS, OR 0.680, CI 0.146-3.178, p=0.6229). Wound infections (including superficial and deep infections) were more common in FS recipients (thirteen FS vs four MS, OR 0.312, CI 0.097-1.005, p=0.0511). Deep sternal wound infection developed in one MS and one FS recipient, neither of whom required plastic surgical repair.

Economic analyses are summarised in Table 4. There was additional cost for MS relative to FS (£1,714 per patient, p=0.0765) in the first year following surgery. MS patients had (non-significant) better EQ-5D-based QALYs (0.03 per patient, p=0.1509). The incremental cost per QALY gained was £61,379, but after adjusting for baseline characteristics, MS had higher costs and lower QALYs (i.e. was dominated). In deterministic and probabilistic sensitivity analyses, MS was either dominated or had a very large cost per QALY, except for the complete case analysis (Appendix B. Tables B11, B12).

Discussion

The UK NHS is a free for patient at point-of-delivery healthcare system. Apart from good recovery, hospital discharge of a significant proportion of elderly patients depends on the timely availability of social care services in the community. ~~for a significant proportion of elderly patients, hospital discharge depends on the timely availability of social care services in the community~~. The Mini-Stern trial is the first RCT comparing ~~the effect of~~ FS and MS ~~approaches~~ for isolated AVR when performed for UK NHS patients.

In this prospective, pragmatic, open-label RCT, MS ~~approach~~ did not reduce the total duration of hospital stay after AVR. As hospital discharge is sometimes delayed due to social factors, we included time until fit for ~~hospital~~ discharge as a second primary endpoint. This was also not reduced by MS ~~approach~~. These ~~primary~~ endpoints were recorded by physiotherapists based on a common discharge protocol with specific clinical milestones to achieve, thereby excluding ~~which excluded~~ physician-induced bias.

In this study ~~we have demonstrated that MS approach recorded significantly greater~~ operation, total theatre, aortic cross-clamp and CPB times were significantly prolonged with MS. This was expected as in general, minimal access valve operations take longer [5, 9].

~~compared to conventional approach.~~ Th~~is~~ is ~~e prolonged operation time, total theatre, cross-clamp and CPB times associated with MS approach is~~ justifiable if MS ~~it~~ resulted in either faster recovery, shorter postoperative stay, reduced cost of treatment or more importantly a significant reduction in adverse events and therefore superior patient safety. In this RCT, MS did not achieve these benefits and hence we feel that the prolonged operation time, total theatre, cross-clamp and CPB times are not justifiable for performing AVR through ~~a~~ MS. ~~approach.~~

Previously, two meta-analyses [11, 12] concluded that mAVR approaches are superior in certain~~some~~ aspects of postoperative recovery. However, both included studies on mini-thoracotomy approach for AVR, and therefore inferences drawn cannot be extrapolated to MS. ~~Recently a~~A retrospective propensity~~-~~ matched analysis of data from a UK national database concluded that MS ~~mini-sternotomy approach for AVR~~ is safe and comparable to conventional AVR [14]. The authors found ~~that~~ thatMS~~mini-sternotomy approach~~ resulted in a shorter postoperative hospital stay, which disagrees with our findings. However, a propensity-matched study can suffer from selection bias if its matching algorithm produces treatment groups that are unbalanced in some unobserved characteristics. Recently, a retrospective study demonstrated safety of right thoracotomy minimally invasive isolated and concomitant AVR in patients of all age groups [25]. As r~~R~~andomisation balances study groups in known and unknown characteristics, ~~therefore results of the~~ results of the Mini-Stern ~~Mini-Stern~~ trial ~~-~~should be more reliable than non-randomised studies. ~~. The authors of this study concluded that a well-conducted and adequately powered prospective RCT is essential before wider adoption of MS approach for AVR.~~

Previous studies investigating cost-effectiveness provided unclear answers. A report analysing registry data from patients who underwent isolated primary AVR [265] reported lower hospital cost when AVR was performed through right anterior thoracotomy compared to sternotomy-based approaches with no significant differences in outcome. The main reasons attributed to lower costs were earlier hospital discharge and reduced use of blood products. Ghanta et al [276] noted that exclusion of rehabilitation costs could alter this finding. A review by Glauber et al [13], based on uncontrolled studies, noted that higher cost of instruments and devices in mAVR could be offset by economic advantage gained by shorter hospital stay and lower complication rates. The Mini-Stern trial ~~Mini-Stern trial~~ assessed cost-effectiveness using a range of sensitivity analyses, but only the complete case analysis showed MS to be cost-effective, suggesting lower costs but slightly worse outcomes with ~~in~~ MS. ~~patients.~~ However, this analysis used a potentially unrepresentative sample of just 90 patients. Our analysis was restricted to the first year following operation without long-term analysis beyond 1 year.

This RCT is robust with many merits~~strengths~~ including on-table randomisation, comprehensive and independent outcome assessment without physician~~/researcher~~-bias, ~~and~~ longer-term clinical assessment, HRQoL analysis and economic analysis. ~~than previous studies.~~ However there were some limitations. Although we report on secondary endpoints, this trial was powered only to address the primary endpoint. ~~.~~ A total of 14 patients (12%) allocated to MS received FS, which could be another limitation. However, only 6 patients (5%) had true conversion after an attempted MS, while 8 patients (6.7%) went on to FS for safety reasons. Although this ~~This~~ RCT took place in only two centres, thereby limiting

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generalisability, recruitment by eight surgeons improves generalisability. ~~. However, in total eight surgeons recruited patients into the trial which improved generalisability.~~ A total of 1024 patients were screened to recruit 222 (21.7%) patients. Although this potentially suggests selection bias, only 125 eligible patients (12.2%) failed recruitment while the remaining 667 patients (65.1%) did not meet inclusion criteria. Blinding ~~Blinding~~ was not practical as sternotomy dressings were usually changed 48 hours after surgery and patients ~~would~~ bec~~a~~ome aware of the ~~surgical~~ approach. This could have caused bias in self-reported outcomes. Missing 'pain at rest' data were unlikely to be missing at random, and therefore imputation might not have addressed all potential biases. Despite having two primary outcomes, we did not adjust for multiple testing. However, as neither showed a significant difference between groups, this would not have affected our conclusions.

In conclusion, MS for AVR did not result in quicker recovery or earlier hospital discharge. MS resulted in ~~quired~~ longer operations, ~~duration of surgical procedures and~~ increased costs, and resulted in more SAEs than FS. Overall, this pragmatic RCT did not provide evidence that MS results in better clinical or quality of life outcomes, or that MS is cost-effective~~,~~ ~~when~~ compared to FS in the first year after AVR.

Acknowledgement:

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Legends

Central Picture Legend: Duration of hospital stay after AVR: FS versus MS.

Video Legend: MS approach for AVR.

Figure 1. Trial flow diagram.

Figure 2. Kaplan-Meier curves for primary endpoints. Points indicate censoring and dashed lines represent 95% confidence intervals.

Figure 3. Forest plot of HRs and 95% confidence intervals from Cox models.

Figure 4. Cost-effectiveness planes. Proportion of points below each threshold gives the probability that MS is more cost-effective than FS. This probability is 3.7% for willingness to pay £20,000/QALY and 5.1% for willingness to pay £30,000/QALY.

Table 1. Baseline characteristics

	MS (n = 118)	FS (n = 104)
Age (years) - Mean (SD)	71.3 (12.3)	72.1 (10.9)
BMI (kg/m^2) – Mean (SD)	26.6 (3.2)	27.7 (3.7)
Sex - frequency (%)		
Female	53 (45%)	57 (55%)
Male	65 (55%)	47 (45%)
Valve type - frequency (%)		
Mechanical	15 (13%)	14 (13%)
Tissue	103 (87%)	90 (87%)
EuroSCORE (%) - Mean (SD)	5.9 (2.1) *	6.1 (2.1)

* EuroSCORE was missing for one MS patient.

491 **Table 2. Kaplan-Meier medians (quartiles) for time-to-event endpoints**

	MS (n = 118)	FS (n = 104)	p-value*
Time to discharge (days)	7 (6, 10)	7 (6, 10)	0.6924
Censored	3	1	
Time until fit for discharge (days)	6 (5, 10)	6 (5, 9)	0.5597
Censored	10	7	
Time to independent~~first~~ mobilisation (days)	4 (3, 7)	4 (3, 6)	0.5819
Censored	8	7	
Time to mediastinal drain removal (hours)	26.1 (20.6, 53.3)	22.5 (19.4, 37.8)	0.0157
Censored	2	2	
Time to extubation (hours)	9.2 (7.8, 12.1)	8.3 (6.8, 11.7)	0.5488
Censored	1	1	
Theatre time (minutes)	191 (172, 225)	176 (152, 203)	< 0.0001
Censored	0	0	
CPB time (minutes)	80 (70, 95)	66 (52, 85)	< 0.0001
Censored	0	0	
Cross-clamp time (minutes)	65 (53, 76)	49 (39, 64)	< 0.0001
Censored	0	0	
Surgery duration (minutes)	163 (139, 190)	149 (114, 167)	< 0.0001
Censored	3	4	

492 **Log-rank test. Seven surgery durations were not recorded and censored at 1 minute.*

493

Table 3. Costs, QALYs and eCost-effectiveness

	Cost and QALYs (with imputation)	FS (n = 118)		MS (n = 104)	
		Mean Cost per patient	SD	Mean Cost per patient	SD
Primary Admission Costs	Theatre use	£3,824	£1,243	£4,422	£2,053
	Additional surgical items	£16.52	£0.0	£52.0	£0.0
	Critical care (ITU)	£1,834	£3,023	£2,934	£5,030
	Cardiac ward	£2,744	£1,664	£2,676	£1,500
	Physio- and Occupational Therapy	£77	£55	£78	£68
	Rehabilitation	£384	£1,878	£263	£1,621
	Acute hospital	£347	£1,919	£298	£1,971
	Sub-total cost	*£9,226*	*£6,511*	*£10,724*	*£8,850*
Post primary admission costs to 12 months	Hospital Re-admission	£418	£1,475	£575	£1,863
	Follow up tests	£224	£258	£282	£279
	Follow up healthcare visits	£373	£359	£311	£263
	Sub-total cost	*£1,015*	*£1,778*	*£1,168*	*£2,079*
	Drugs	£379	£548	£441	£977
	Total cost over 12 months	*£10,620*	*£7,624*	*£12,333*	*£9,864*
Incremental cost-effectiveness* (probabilistic analysis with	Incremental cost at 12 months (MS-FS)			£2,154.0 (*SE* £36)	
	Incremental EQ-5D-3L QALYs (MS-FS)			-0.0122 (SE 0.0008)	
	ICER			MS dominated by FS	
	NMB (at WTP £20,000/QALY)			-£2,397	
	NMB (at WTP £30,000/QALY)			-£2,519	

baseline adjustment)
SD: standard deviation, SE: standard error, WTP: willingness to pay, NMB: net monetary benefit, ICER: incremental cost-effectiveness ratio. * Incremental costs and effects estimated using SUR, adjusting for baseline differences.

~~QALYs and cost-effectiveness~~

496

	Cost and QALYs (with imputation)	FS (n = 118)		MS (n = 104)	
		Mean Cost per patient	SD	Mean Cost per patient	SD
Primary Admission Costs	Theatre use	£3,824	£1,243	£4,422	£2,053
	Additional surgical items	£16.52	£0.0	£52.0	£0.0
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	Drugs	£379	£548	£441	£977
	Total cost over 12 months	*£10,620*	*£7,624*	*£12,333*	*£9,864*
Incremental cost-effectiveness* (probabilistic analysis with baseline adjustment)	Incremental cost at 12 months (MS-FS)	£2,154.0 (*SE* £36)			
	Incremental EQ-5D-3L QALYs (MS-FS)	-0.0122 (SE 0.0008)			
	ICER	MS dominated by FS			
	NMB (at WTP £20,000/QALY)	-£2,397			
	NMB (at WTP £30,000/QALY)	-£2,519			

SD: standard deviation, SE: standard error WTP: willingness to pay, NMB: net monetary benefit, ICER: incremental cost-effectiveness ratio. * Incremental costs and effects estimated using SUR, adjusting for baseline differences.

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Appendices

Tables and figures:

Appendix A: Statistical Analysis

Table A1. All patients who underwent a redo sternotomy, or crossed over from mini- to full sternotomy, or were randomised but found to be ineligible

	Allocated treatment	Description	Per-protocol population	Safety population
Redos	FS	Return to theatre for ventricular septal defect closure and redo-AVR.	As FS	As FS
	FS	Return to theatre for tamponade and cardiac arrest. Redo sternotomy for tamponade.	As FS	As FS
	MS	Return to theatre for tamponade MA bleed. Conversion to FS.	As MS	As MS
	MS	Return to theatre for bleeding. Redo FS.	As MS	As MS
	MS	Return to theatre for tamponade. Evacuation of clot/pericardial effusion. Conversion to FS.	As MS	As MS
	MS	Return to theatre for cardiac arrest and tamponade. Emergency re-sternotomy (FS), tamponade and aortotomy repair.	As MS	As MS
	MS	Return to theatre for pericardial collection and early tamponade. PEA arrest. Re-exploration on bypass. Completion FS.	As MS	As MS
	MS	Second return to theatre. Attempted weaning of ECMO and placement of RVAD. Removal of blood clot. Redo sternotomy.	As MS	As MS
Crossovers	MS	Aortic root replacement required, FS indicated.	Excluded	As FS
	MS	FS indicated as unable to perform TOE.	Excluded	As FS
	MS	Aorta interposition graft required.	Excluded	As MS
	MS	FS indicated as unable to have TOE.	Excluded	As FS
	MS	Needed CABG due to intraoperative injury.	Excluded	As MS
	MS	Needed CABG due to intraoperative injury.	Excluded	As MS
	MS	FS indicated as unable to perform TOE.	Excluded	As FS
	MS	Required aortic root replacement, conversion to FS.	Excluded	As MS
	MS	Patient randomised too early - unable to insert TOE probe.	Excluded	As FS
	MS	Did not have correct equipment in theatre.	Excluded	As FS
	MS	Mini-sternotomy equipment not available.	Excluded	As FS
	MS	Bleeding.	Excluded	As MS
	MS	Patient had calcified aorta. Nowhere to cannulate safely.	Excluded	As MS
Ineligible	FS	Withdrawn from trial by surgeon pre-operatively (but post-randomisation) as required AVR and myectomy.	Excluded	Excluded
	FS	Poor quality baseline echocardiogram, with no assessment of LV function.	Excluded	As FS
	MS	Surgeon had not checked echo report until after randomisation. Underwent FS.	Excluded	As FS

Table A2. Additional summaries of in-hospital endpoints

	Mini-sternotomy (n = 118)	Full sternotomy (n = 104)
Time to discharge (days)		
Mean (standard error)	9.5 (0.6)	8.6 (0.5)
Median (95% confidence interval)	7 (6, 8)	7 (6, 8)
Time until fit for discharge (days)		
Mean (standard error)	8.5 (0.5)*	7.5 (0.3)*
Median (95% confidence interval)	6 (5, 7)	6 (6, 7)
Time to first mobilisation (days)		
Mean (standard error)	5.7 (0.5)*	4.9 (0.3)*
Median (95% confidence interval)	4 (3, 4)	4 (-, -)
Time to mediastinal drain removal (hours)		
Mean (standard error)	48.1 (4.8)*	30.0 (1.7)
Median (95% confidence interval)	26.1 (22.8, 42.6)	22.5 (22.0, 22.9)
Time to first extubation (hours)		
Mean (standard error)	13.1 (1.7)*	10.5 (0.7)
Median (95% confidence interval)	9.2 (8.7, 9.9)	8.3 (8.0, 9.2)

Table A2 shows Kaplan-Meier estimates of in-hospital endpoints. Censoring of longest time to event for some endpoints led to underestimation of means and standard errors (highlighted with asterisks). A confidence interval for median time to mobilisation could not be estimated.

Table A3. Additional summaries of operative endpoints

	Mini-sternotomy (n = 118)	Full sternotomy (n = 104)
Theatre time (minutes)		
Mean (standard error)	201.2 (3.9)	181.0 (4.6)
Median (95% confidence interval)	191 (187, 205)	176 (170, 180)
CPB time (minutes)		
Mean (standard error)	82.0 (1.9)	69.5 (2.3)
Median (95% confidence interval)	80 (77, 86)	66 (59, 74)
Cross clamp time (minutes)		
Mean (standard error)	65.5 (1.5)	52.4 (1.6)
Median (95% confidence interval)	65 (61, 69)	49 (45, 53)
Surgery duration (minutes)		
Mean (standard error)	165.5 (3.4)	145.7 (4.3)
Median (95% confidence interval)	163(155, 172)	148.5 (134, 153)
Total theatre time, including repeats/readmissions (minutes)		
Mean (standard error)	221.1 (9.5)	191.2 (6.1)
Median (95% confidence interval)	196 (189, 210)	178.5 (171, 188)
Total CPB time, including repeats/readmissions (minutes)		
Mean (standard error)	85.1 (2.6)	71.1 (2.8)
Median (95% confidence interval)	82 (77, 87)	66 (59, 74)
Total cross clamp time, including repeats/readmissions (minutes)		
Mean (standard error)	66.1 (1.6)	53.5 (2.0)
Median (95% confidence interval)	66 (61, 70)	49 (45, 53)
Volume of blood lost in the first 12 postoperative hours (ml)		
Mean (SD)	310.4 (342.5)	323.2 (267.8)
Median (quartiles)	225 (150, 325)	250 (175, 375)
Transfusion of packed red cells in the first 48 postoperative hours (ml)		
Number of transfused patients (%)	50 (42%)	51 (49%)
Mean (SD) in transfused patients	625.3 (513.2)	442.4 (265.3)
Median (quartiles) in transfused patients	500 (300, 644)	303 (284, 569)
Transfusion of clotting products in the first 48 postoperative hours (ml)		
Number of transfused patients (%)	11 (9%)	4 (4%)
Mean (SD) in transfused patients	920.5 (1438.4)	753.0 (672.5)
Median (quartiles) in transfused patients	332 (183, 1050)	625 (209, 1297)

All estimates for time-to-event endpoints in Table A3 are Kaplan-Meier estimates. Time data were complete, except for seven surgery durations (3 MS, 4 FS) that were not recorded and were therefore censored at 1 minute. Blood data were only missing for one patient (FS group, withdrawn before surgery). Blood transfusion and clotting products data for seven patients at the Freeman hospital were recorded in units and converted to ml (1 unit PRC = 300ml, 1 unit platelets = 245ml, 1 unit FFP = 280ml). Transfusion data were explored using logistic regression models, including fixed effects for treatment, valve and sex, and a random surgeon effect. These analyses did not show a statistically significant difference between MS and FS patients in either need for blood transfusion (MS/FS odds ratio 0.797, confidence interval 0.453 to 1.402, p-value 0.4310) or the need for transfusion of clotting products (MS/FS odds ratio 2.616, confidence interval 0.801 to 8.541, p-value 0.1112).

Table A4. Results from Cox models and log-rank tests for primary and secondary endpoints

	MS/FS hazard ratio (95% confidence interval)	p-value for null hypothesis HR = 1	Log-rank test statistic	p-value from log-rank test
Primary analyses				
Time to discharge	0.874 (0.668,1.143)	0.3246	0.157	0.6924
Time until fit	0.907 (0.688,1.197)	0.4914	0.340	0.5597
Per protocol analyses of primary endpoints				
Time to discharge	0.868 (0.656,1.147)	0.3194	0.200	0.6544
Time until fit	0.915 (0.688,1.218)	0.5443	0.217	0.6415
Sensitivity analyses: age included as an effect in the Cox models				
Time to discharge	0.866 (0.661,1.135)	0.2985	0.157	0.6924
Time until fit	0.902 (0.683,1.192)	0.4685	0.340	0.5597
Sensitivity analyses: EuroSCORE included as an effect in the Cox models				
Time to discharge	0.885 (0.676,1.159)	0.3753	0.157	0.6924
Time until fit	0.936 (0.709,1.236)	0.6400	0.340	0.5597
Sensitivity analyses: censoring times taken as event times:				
Time to discharge	0.884 (0.677,1.153)	0.3625	0.189	0.6639
Time until fit	0.888 (0.680,1.160)	0.3844	0.765	0.3819
Sensitivity analysis: patients assumed to be fit at discharge				
Time until fit	0.879 (0.671, 1.151)	0.3480	0.703	0.4018
Secondary endpoint analyses				
Time until first mobilisation	0.899 (0.680,1.187)	0.4518	0.303	0.5819
Time until drain removal	0.587 (0.442,0.778)	0.0002	5.838	0.0157
Time until first extubation	0.856 (0.655,1.120)	0.2582	0.359	0.5488
Exploratory analyses				
Surgery duration	0.660 (0.500,0.872)	0.0035	17.892	< 0.0001
CPB time	0.592 (0.448,0.782)	0.0002	24.871	< 0.0001
Cross clamp time	0.451 (0.340,0.597)	< 0.0001	42.539	< 0.0001
Theatre time	0.665 (0.503,0.879)	0.0042	16.806	< 0.0001
Total CPB time including repeats/readmissions	0.547 (0.414,0.723)	< 0.0001	20.176	< 0.0001
Total cross clamp time including repeats/readmissions	0.458 (0.346,0.608)	< 0.0001	34.352	< 0.0001
Total theatre time including repeats/readmissions	0.698 (0.531,0.918)	0.0102	5.657	0.0174
Time to death by any cause	1.871 (0.723, 4.844)	0.1966	0.7309	0.3926

Table A4 shows the results of all analyses performed for the primary and secondary time-to-event endpoints, including unplanned, exploratory analyses of secondary endpoints. All secondary endpoint analyses, sensitivity analyses and exploratory analyses were performed using the intent to treat population. All log-rank tests were stratified by valve, sex and surgeon. All Cox models included valve, sex and treatment as fixed effects, and surgeon as a random effect. Exploratory analysis of time to all-cause death included age as a fixed effect in the Cox model. Mean imputation was used for missing EuroSCORE data at baseline (1 MS).

Table A5. Summaries of pain at rest scores in the first ten days following surgery

		Mini-sternotomy (n = 118)	Full sternotomy (n = 104)
Day 1	Mean (SD)	3.5 (2.5)	3.7 (2.4)
	n	100 (85%)	82 (80%)
Day 2	Mean (SD)	3 (2.3)	3.1 (2.5)
	n	89 (75%)	81 (79%)
Day 3	Mean (SD)	2.7 (2.3)	2.4 (2.3)
	n	91 (77%)	83 (81%)
Day 4	Mean (SD)	2.4 (2.1)	2.4 (2.4)
	n	94 (80%)	84 (82%)
Day 5	Mean (SD)	2 (1.9)	2.1 (2)
	n	90 (79%)	80 (79%)
Day 6	Mean (SD)	1.8 (1.7)	2.1 (2)
	n	69 (77%)	61 (76%)
Day 7	Mean (SD)	1.5 (1.8)	1.8 (2)
	n	46 (69%)	42 (78%)
Day 8	Mean (SD)	1.2 (1.4)	1.7 (1.6)
	n	40 (77%)	35 (76%)
Day 9	Mean (SD)	1 (1.8)	0.8 (1.5)
	n	25 (57%)	18 (47%)
Day 10	Mean (SD)	0.7 (1)	1.3 (2)
	n	18 (47%)	12 (43%)

Table A5 shows the number of pain scores taken for each of the 10 days following surgery. The denominator used for each percentage is the number of patients known to be alive and in hospital on the given day.

Table A6. Summaries of EQ-5D utility scores up to the 12 month follow-up

		Mini-sternotomy (n = 118)	Full sternotomy (n = 104)
Baseline	Mean (SD)	0.77 (0.19)	0.70 (0.24)
	n	105 (89%)	95 (91%)
Day 4	Mean (SD)	0.47 (0.29)	0.39 (0.28)
	n	92 (78%)	89 (86%)
Discharge	Mean (SD)	0.60 (0.24)	0.58 (0.24)
	n	103 (87%)	88 (85%)
Six weeks	Mean (SD)	0.74 (0.23)	0.71 (0.21)
	n	106 (90%)	88 (85%)
Six months	Mean (SD)	0.83 (0.25)	0.83 (0.23)
	n	105 (89%)	95 (91%)
Twelve months	Mean (SD)	0.83 (0.29)	0.78 (0.28)
	n	103 (87%)	84 (81%)

For patients who died, EQ-5D scores were taken to be zero following death. Percentages presented in Table A6 were calculated as the number of scores recorded (including the zeros) divided by the number of patients randomised to the group. The difference in mean baseline score was potentially due to the imbalance in gender (the FS group has a greater proportion of females, who reported lower quality of life on average).

Table A7. Summaries of SF-36 domain scores up to the 12 month follow up

			Mini-sternotomy (n = 118)	Full sternotomy (n = 104)
Bodily pain	Baseline	Mean (SD)	70 (25)	64 (28)
		n	104 (88%)	96 (92%)
	Six weeks	Mean (SD)	61 (24)	60 (23)
		n	105 (89%)	90 (87%)
	Six months	Mean (SD)	79 (27)	74 (28)
		n	104 (88%)	94 (90%)
	Twelve months	Mean (SD)	76 (31)	72 (32)
		n	99 (84%)	86 (83%)
General health	Baseline	Mean (SD)	62 (20)	58 (22)
		n	104 (88%)	94 (90%)
	Six weeks	Mean (SD)	70 (20)	66 (20)
		n	104 (88%)	91 (88%)
	Six months	Mean (SD)	71 (24)	66 (24)
		n	103 (87%)	94 (90%)
	Twelve months	Mean (SD)	68 (26)	62 (26)
		n	100 (85%)	86 (83%)
Mental health	Baseline	Mean (SD)	74 (18)	67 (21)
		n	104 (88%)	95 (91%)
	Six weeks	Mean (SD)	72 (22)	73 (19)
		n	104 (88%)	91 (88%)
	Six months	Mean (SD)	80 (21)	74 (22)
		n	103 (87%)	94 (90%)
	Twelve months	Mean (SD)	76 (26)	73 (23)
		n	100 (85%)	86 (83%)
Physical functioning	Baseline	Mean (SD)	54 (26)	47 (28)
		n	105 (89%)	96 (92%)
	Six weeks	Mean (SD)	63 (22)	56 (23)
		n	105 (89%)	91 (88%)
	Six months	Mean (SD)	78 (27)	70 (28)
		n	104 (88%)	94 (90%)
	Twelve months	Mean (SD)	74 (30)	67 (31)
		n	100 (85%)	86 (83%)
Role emotional	Baseline	Mean (SD)	67 (40)	55 (46)
		n	104 (88%)	94 (90%)
	Six weeks	Mean (SD)	60 (44)	63 (43)
		n	104 (88%)	90 (87%)
	Six months	Mean (SD)	81 (35)	72 (42)
		n	104 (88%)	94 (90%)
	Twelve months	Mean (SD)	76 (39)	71 (42)
		n	98 (83%)	85 (82%)
Role physical	Baseline	Mean (SD)	33 (41)	23 (38)
		n	103 (87%)	96 (92%)

	Six weeks	Mean (SD)	19 (32)	20 (33)
		n	103 (87%)	90 (87%)
	Six months	Mean (SD)	65 (42)	59 (44)
		n	103 (87%)	94 (90%)
	Twelve months	Mean (SD)	64 (44)	52 (46)
		n	98 (83%)	85 (82%)
Social functioning	Baseline	Mean (SD)	66 (30)	61 (29)
		n	104 (88%)	94 (90%)
	Six weeks	Mean (SD)	66 (29)	68 (27)
		n	104 (88%)	91 (88%)
	Six months	Mean (SD)	85 (26)	78 (28)
		n	102 (86%)	93 (89%)
	Twelve months	Mean (SD)	81 (30)	78 (30)
		n	98 (83%)	85 (82%)
Vitality	Baseline	Mean (SD)	46 (25)	40 (23)
		n	104 (88%)	95 (91%)
	Six weeks	Mean (SD)	50 (22)	48 (22)
		n	104 (88%)	90 (87%)
	Six months	Mean (SD)	64 (23)	57 (23)
		n	103 (87%)	94 (90%)
	Twelve months	Mean (SD)	60 (26)	54 (26)
		n	100 (85%)	86 (83%)

An in-house implementation of the standard scoring algorithm for the developmental version of SF-36 was used. For patients who died, SF-36 scores were taken to be zero following death. Percentages presented in Table A7 were calculated as the number of scores recorded (including the zeros) divided by the number of patients randomised to the group. The differences in mean baseline scores were potentially due to the imbalance in gender (the FS group has a greater proportion of females, who reported lower quality of life on average).

Table A8. Estimated treatment effects (MS - FS) and treatment-time interactions for SF-36 domain scores up to 12 months, EQ-5D utility scores up to 12 months and pain scores up to discharge

	Effect (MS – FS)	95% confidence interval	p-value
Pain at rest (n = 219)			
Treatment effect	0.0	(-0.7, 0.6)	0.9766
Treatment-time (days) interaction	0.0	(-0.1, 0.1)	0.8190
EQ-5D utility scores (n = 197)			
Treatment effect	0.02	(-0.03, 0.07)	0.5148
Treatment-time (months) interaction	0.00	(-0.01, 0.01)	0.9731
SF-36 physical functioning (n = 192)			
Treatment effect	1.2	(-6.2, 8.7)	0.7414
Treatment-time (months) interaction	0.3	(-0.2, 0.9)	0.2387
SF-36 role physical (n = 190)			
Treatment effect	-8.3	(-21.1, 4.5)	0.2025
Treatment-time (months) interaction	1.7	(0.3, 3.1)	0.0169
SF-36 bodily pain (n = 191)			
Treatment effect	-0.7	(-9.1, 7.8)	0.8792
Treatment-time (months) interaction	0.3	(-0.5, 1.1)	0.4331
SF-36 general health (n = 189)			
Treatment effect	-1.0	(-7.5, 5.5)	0.7710
Treatment-time (months) interaction	0.3	(-0.2, 0.8)	0.2224
SF-36 vitality (n = 190)			
Treatment effect	-2.1	(-8.8, 4.5)	0.5273
Treatment-time (months) interaction	0.6	(0.1, 1.2)	0.0293
SF-36 social functioning (n = 189)			
Treatment effect	-5.5	(-14.1, 3.1)	0.2093
Treatment-time (months) interaction	1.0	(0.2, 1.7)	0.0183
SF-36 role emotional (n = 189)			
Treatment effect	-6.2	(-18.6, 6.2)	0.3255
Treatment-time (months) interaction	1.1	(-0.1, 2.3)	0.0699
SF-36 mental health (n = 190)			
Treatment effect	-3.2	(-9.7, 3.4)	0.3431
Treatment-time (months) interaction	0.5	(-0.0, 1.0)	0.0702

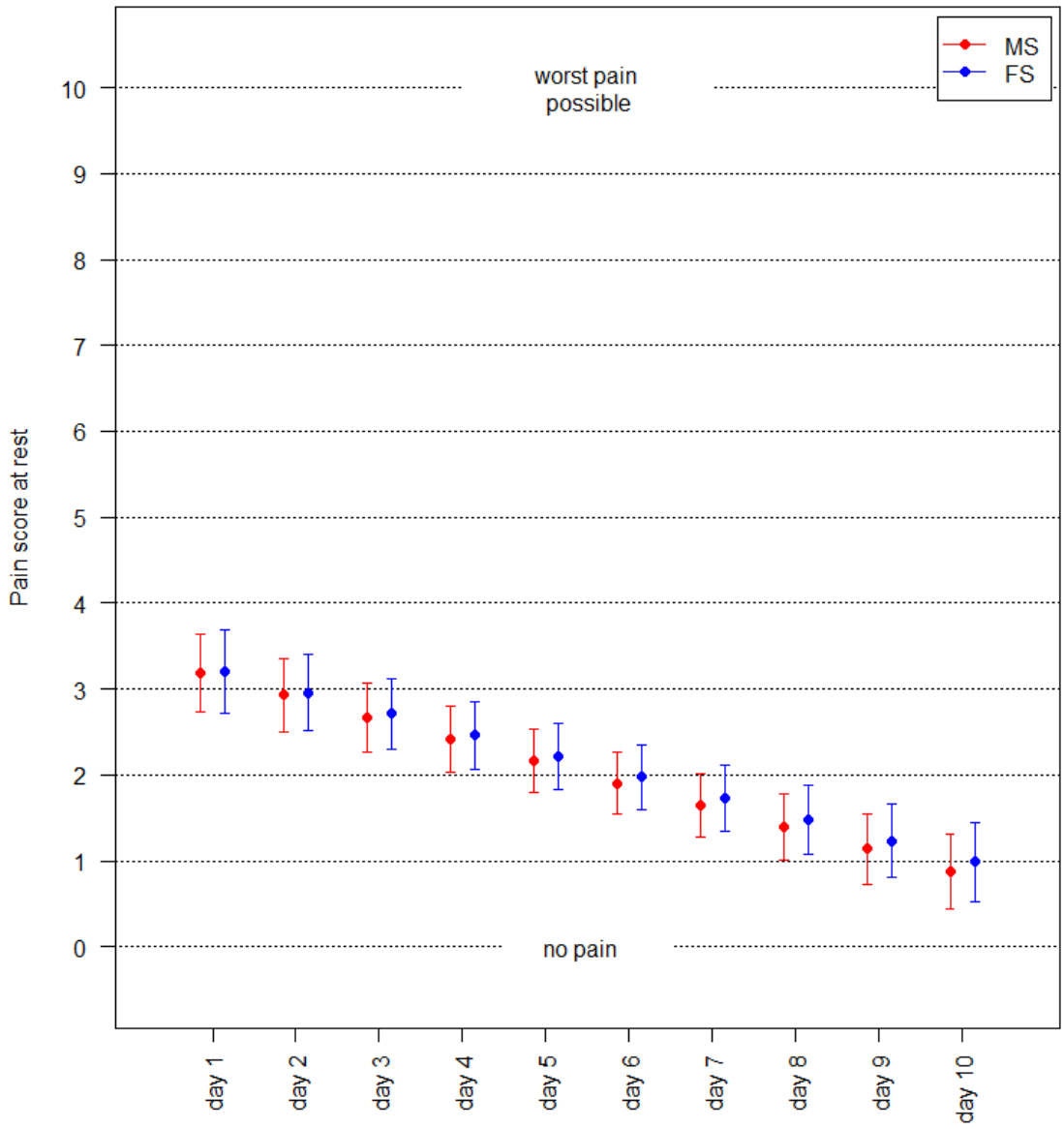
Table A8 shows results of complete case analyses of questionnaire data, under a missing completely at random assumption, including only patients with at least one analysable follow-up questionnaire. For each analysis, the n in parentheses is number of patients used to fit the model. For pain and SF-36 scores, some random effects were estimated to have a variance of 0 and were excluded from the models (surgeon effect for pain, and both the surgeon effect and random slope for SF-36). The slope (time coefficient) was estimated to be negative for pain and positive for all EQ-5D and SF-36 scores. This suggests improvement over time in each score. Evidence of greater rate of improvement over time for MS patients (statistically significant, positive interaction term) was seen for three SF-36 domains (role physical, vitality, and social functioning), but no others.

Table A9. Estimated treatment effects (MS-FS) and treatment-time interactions for SF-36 domain scores up to 12 months, EQ-5D utility scores up to 12 months and pain scores up to discharge, after multiple imputation of missing scores

	Effect (MS – FS)	95% confidence interval	p-value
Pain at rest			
Treatment effect	0.0	(-0.7, 0.6)	0.9059
Treatment-time (days) interaction	0.0	(-0.1, 0.1)	0.9685
EQ-5D utility scores			
Treatment effect	0.01	(-0.04, 0.06)	0.8203
Treatment-time (months) interaction	0.00	(-0.01, 0.01)	0.9094
SF-36 physical functioning			
Treatment effect	2.0	(-4.9, 8.9)	0.5744
Treatment-time (months) interaction	0.2	(-0.3, 0.8)	0.3996
SF-36 role physical			
Treatment effect	-6.6	(-18.7, 5.4)	0.2808
Treatment-time (months) interaction	1.5	(0.1, 2.8)	0.0310
SF-36 bodily pain			
Treatment effect	-0.1	(-9.0, 7. 7)	0.9748
Treatment-time (months) interaction	0.3	(-0.4, 1.1)	0.4091
SF-36 general health			
Treatment effect	1.1	(-5.0, 7.3)	0.7175
Treatment-time (months) interaction	0.2	(-0.3, 0.7)	0.3373
SF-36 vitality			
Treatment effect	-0.5	(-6.9, 5.9)	0.8798
Treatment-time (months) interaction	0.4	(-0.2, 1.0)	0.1733
SF-36 social functioning			
Treatment effect	-4.4	(-12.4, 3.5)	0.2756
Treatment-time (months) interaction	0.7	(0.0, 1.5)	0.0589
SF-36 role emotional			
Treatment effect	-4.6	(-16.4, 7.2)	0.4415
Treatment-time (months) interaction	0.8	(-0.4, 2.0)	0.1790
SF-36 mental health			
Treatment effect	-2.5	(-8.6, 3.5)	0.4113
Treatment-time (months) interaction	0.4	(-0.1, 0.9)	0.1195

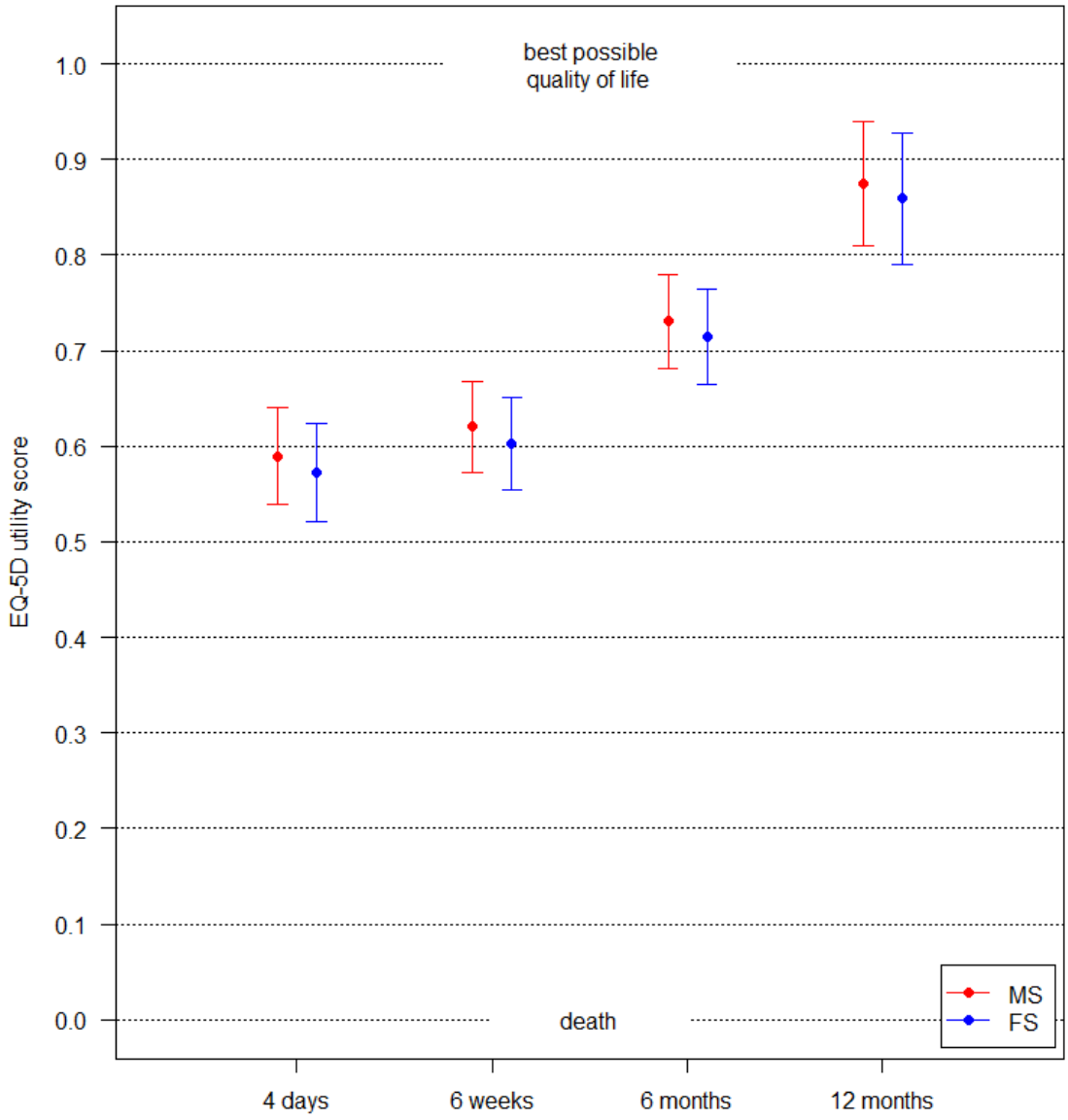
Table A9 shows the results from analysing the questionnaire data using multiple imputation to handle missing observations, under a missing at random assumption. For each analysis, missing data were imputed from models that included all other variables used in the analysis, along with CCS grading and NYHA grading as auxiliary variables. The method used was multiple imputation by chained equations with predictive mean matching. Estimates from 100 imputed data sets were combined using Rubin's rules. Pain was only imputed for patients known to be alive and in hospital, not for patients who had died or had already been discharged. Evidence of greater rate of improvement over time for MS patients (statistically significant, positive interaction term) was seen only for one SF-36 domain.

Figure A1. Forest plots of mean pain scores for the first 10 days following surgery, with 95% confidence intervals



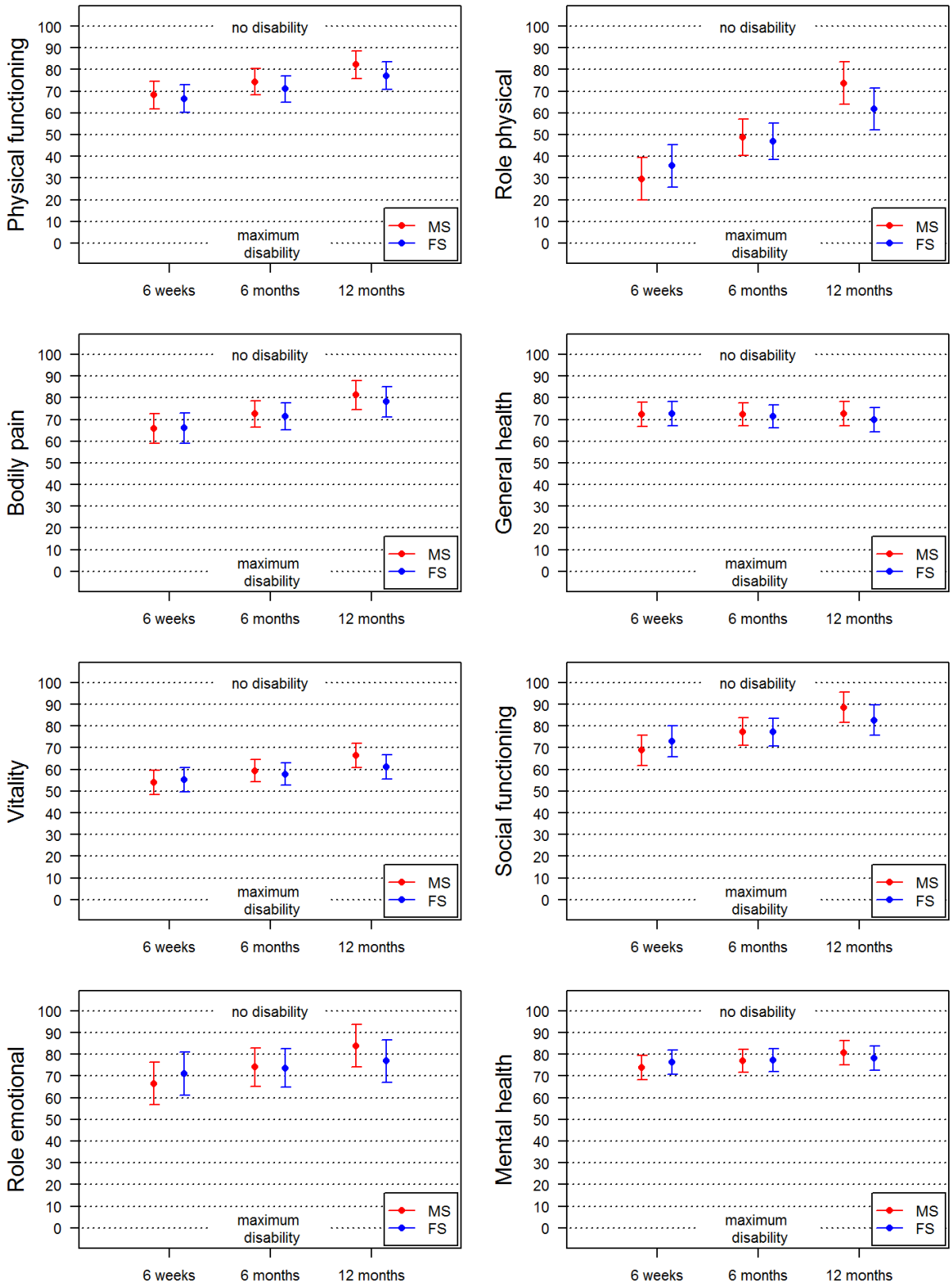
In Figure A1, means on each day were adjusted for sex and valve type, and were estimated from the complete case analysis.

Figure A2. Forest plot of mean EQ-5D scores at each follow-up time, with 95% confidence intervals



In Figure A2, means at each follow-up time were adjusted for baseline EQ-5D, sex and valve type, and were estimated from the complete case analysis.

Figure A3. Forest plot of mean SF36 domain scores at each follow-up time, with 95% confidence intervals



In Figure A3, means at each follow-up time were adjusted for baseline domain score, sex and valve type, and were estimated from the complete case analysis. A score of 100 represents no disability, and a score of 0 represents maximum disability.

Table A10. Summaries heart function (LVEF) and respiratory function (FEV_1)

	Mini-sternotomy (n = 118)	Full sternotomy (n = 104)
FEV_1 (litres):		
Baseline visit		
Mean (SD)	2.3 (0.7)	2.3 (0.8)
Median (quartiles)	2.2 (1.8, 2.7)	2.2 (1.7, 2.6)
n	115	101
Discharge		
Mean (SD)	1.6 (0.6)	1.6 (0.6)
Median (quartiles)	1.5 (1.2, 1.8)	1.5 (1.2, 1.9)
n	82	69
6 week visit		
Mean (SD)	2.1 (0.8)	2.1 (0.7)
Median (quartiles)	2 (1.5, 2.5)	1.9 (1.6, 2.5)
n	92	84
6 month visit		
Mean (SD)	2.2 (0.7)	2.1 (0.7)
Median (quartiles)	2.1 (1.7, 2.6)	1.9 (1.4, 2.4)
n	91	82
LVEF (%):		
Baseline visit		
Mean (SD)	61.9 (9.1)	62.4 (8.6)
Median (quartiles)	62.5 (57.5, 67.5)	63 (57.5, 67.0)
n	117	101
Discharge		
Mean (SD)	59.9 (9.7)	59 (10.2)
Median (quartiles)	62 (55.0, 65.0)	58 (55.0, 64.5)
n	106	96
6 month visit		
Mean (SD)	61.2 (8.1)	61.8 (9.7)
Median (quartiles)	61 (56.0, 67.5)	62.5 (56.3, 68.0)
n	97	88

FEV_1 is forced expiratory volume in one second, measured by hand-held spirometry. LVEF is left ventricular ejection fraction, measured by echocardiography. No analyses were planned for these endpoints.

Table A11. Frequency of non-fatal SAEs (number of patients) within one year of surgery, by treatment received

	Mini-sternotomy (n = 110)	Full sternotomy (n = 111)	Total (n = 221)
Cardiac (including atrial fibrillation, conduction problems, need for permanent pacemaker)	43 (29)	27 (21)	70 (50)
Respiratory	20 (14)	9 (8)	29 (22)
Injury/procedural	19 (11)	7 (6)	26 (17)
Non-cardiorespiratory infection (including wound)	7 (7)	12 (9)	19 (16)
Urinary	11 (10)	8 (6)	19 (16)
Surgical and medical procedures	9 (6)	7 (7)	16 (13)
Nervous system	8 (8)	7 (7)	15 (15)
Cardiorespiratory infection (including endocarditis, device-related infections, chest infection)	9 (9)	6 (5)	15 (14)
Vascular	9 (9)	1 (1)	10 (10)
Psychiatric	5 (5)	5 (5)	10 (10)
Gastro-intestinal – diarrhoea	7 (6)	3 (3)	10 (9)
Gastro-intestinal – other	7 (7)	1 (1)	8 (8)
General disorders	4 (4)	3 (2)	7 (6)
Metabolic	2 (2)	3 (2)	5 (4)
Blood/lymph	4 (3)	1 (1)	5 (4)
Neoplasms	1 (1)	1 (1)	2 (2)
Hepatitis/cholecystitis	1 (1)	1 (1)	2 (2)
Musculoskeletal	2 (2)	0 (0)	2 (2)
Skin/tissue	0 (0)	1 (1)	1 (1)
Eye	0 (0)	1 (1)	1 (1)
Immune	0 (0)	1 (1)	1 (1)
Total	168 (56)	105 (46)	273 (102)

Among the nervous system SAEs recorded in Table A11, strokes were suffered by 3 FS recipients and 2 MS recipients. No patient suffered more than one stroke.

Table A12. Frequencies of non-death SAEs (and number of patients experiencing them), within a year of surgery, at each level of severity, expectedness and relatedness, by treatment received

	Mini-sternotomy (n = 110)	Full sternotomy (n = 111)	Total (n = 221)
Cardiorespiratory:			
Severity			
Severe	26 (14)	14 (11)	40 (25)
Moderate	34 (24)	24 (18)	58 (42)
Mild	12 (11)	4 (4)	16 (15)
Expectedness			
Expected	69 (38)	42 (30)	111 (68)
Unexpected	3 (2)	0 (0)	3 (2)
Relatedness			
Probably related	4 (4)	2 (2)	6 (6)
Possibly related	50 (30)	32 (25)	82 (55)
Unrelated	18 (13)	8 (6)	26 (19)
Total	72 (38)	42 (30)	114 (68)
Non-cardiorespiratory:			
Severity			
Severe	40 (21)	24 (15)	64 (36)
Moderate	43 (29)	31 (21)	74 (50)
Mild	13 (11)	8 (5)	21 (16)
Expectedness			
Expected	68 (34)	45 (27)	113 (61)
Unexpected	28 (15)	18 (15)	46 (30)
Relatedness			
Probably related	9 (5)	5 (5)	14 (10)
Possibly related	37 (22)	30 (20)	67 (42)
Unrelated	50 (27)	28 (20)	78 (47)
Total	96 (41)	63 (34)	159 (75)

The only unexpected events in the MS group were a bilateral pleural effusion in one patient, and bronchial aspiration and peri-arrest event in another. Both patients completely recovered. Exploratory analysis in the safety population, using logistic regression (with fixed treatment, valve and sex effects, and a random surgeon effect), did not show a statistically significant difference between MS and FS recipients in the odds of suffering a non-death SAE within the first year (MS/FS odds ratio 1.559, confidence interval 0.895 to 2.715 and p-value 0.1161). An exploratory Poisson regression (with a fixed effect for treatment and a random patient effect) did show a greater rate of such SAEs for MS recipients (MS/FS rate ratio 1.615, confidence interval 1.070 to 2.437, p-value 0.0225). There were 7 pericardial tamponades in total (4 for FS recipients, 3 for MS recipients, only one per patient), but logistic regression (without the random surgeon effect) did not produce a statistically significant result (MS/FS odds ratio 0.680, confidence interval 0.146 to 3.178, p-value 0.6229).

Table A13. Frequency of paraprosthetic regurgitation, by treatment received

	Mini-sternotomy (n = 110)	Full sternotomy (n = 111)	Total (n = 221)
Discharge			
No regurgitation	84	85	169
Mild regurgitation	19	16	35
Moderate regurgitation	0	0	0
Severe regurgitation	0	0	0
n	101	103	204
6 month visit			
No regurgitation	77	82	159
Mild regurgitation	18	10	28
Moderate regurgitation	0	0	0
Severe regurgitation	0	0	0
n	95	92	187

Paraposthetic regurgitation was explored using logistic regressions at each time point. These were performed as complete case analyses, in the safety population. Logistic regression models included fixed treatment, valve and sex effects, and a random surgeon effect. They did not show a statistically significant difference between MS recipients and FS recipients in the odds of regurgitation, either at discharge (MS/FS odds ratio 1.163, confidence interval 0.553 to 2.445, p-value 0.6883) or at 6 months (MS/FS odds ratio 1.880, confidence interval 0.798 to 4.430, p-value 0.1480).

Table A14. All wound infections within the first year after surgery, by treatment received

Treatment received	Relationship	Description
FS	Possibly related	Superficial sternal wound infection.
FS	Possibly related	Sternal wound infection. Returned to theatre for debridement and 2x wires removed.
FS	Possibly related	Sternal wound infection.
FS	Possibly related	Sternal wound breakdown. Debridement and excision of sinuses. PICC line inserted for 6 weeks IV antibiotics.
FS	Possibly related	Drain site wound infection.
FS	Possibly related	Wound infection - small area at lower end of sternum.
FS	Possibly related	Small sternal wound infection.
FS	Probably related	Sternal wound infection.
FS	Probably related	Sternal wound infection.
FS	Possibly related	Sternal wound infection.
FS	Probably related	Sternal wound infection.
FS	Possibly related	Sternal wound infection. Antibiotics commenced.
FS	Possibly related	Sternal wound infection - requiring hospital admission. Treated with antibiotics.
FS	Possibly related	Wound Infection. Commenced on antibiotics and daily dressings.
MS	Possibly related	Readmission, wound infection, iv/oral flucloxacillin.
MS	Possibly related	MRSA sternal wound infection.
MS	Probably related	Sternal wound infection. Admitted to NGTH with fever, chest pain, SOB and discharging sternal wound. Commenced IV flucloxacillin. Swab taken, VAC dressing applied.
MS	Possibly related	Wound infection at base of sternotomy. Wound swab taken, grown K.pneumoniae. Commenced antibiotics - amoxycillin.

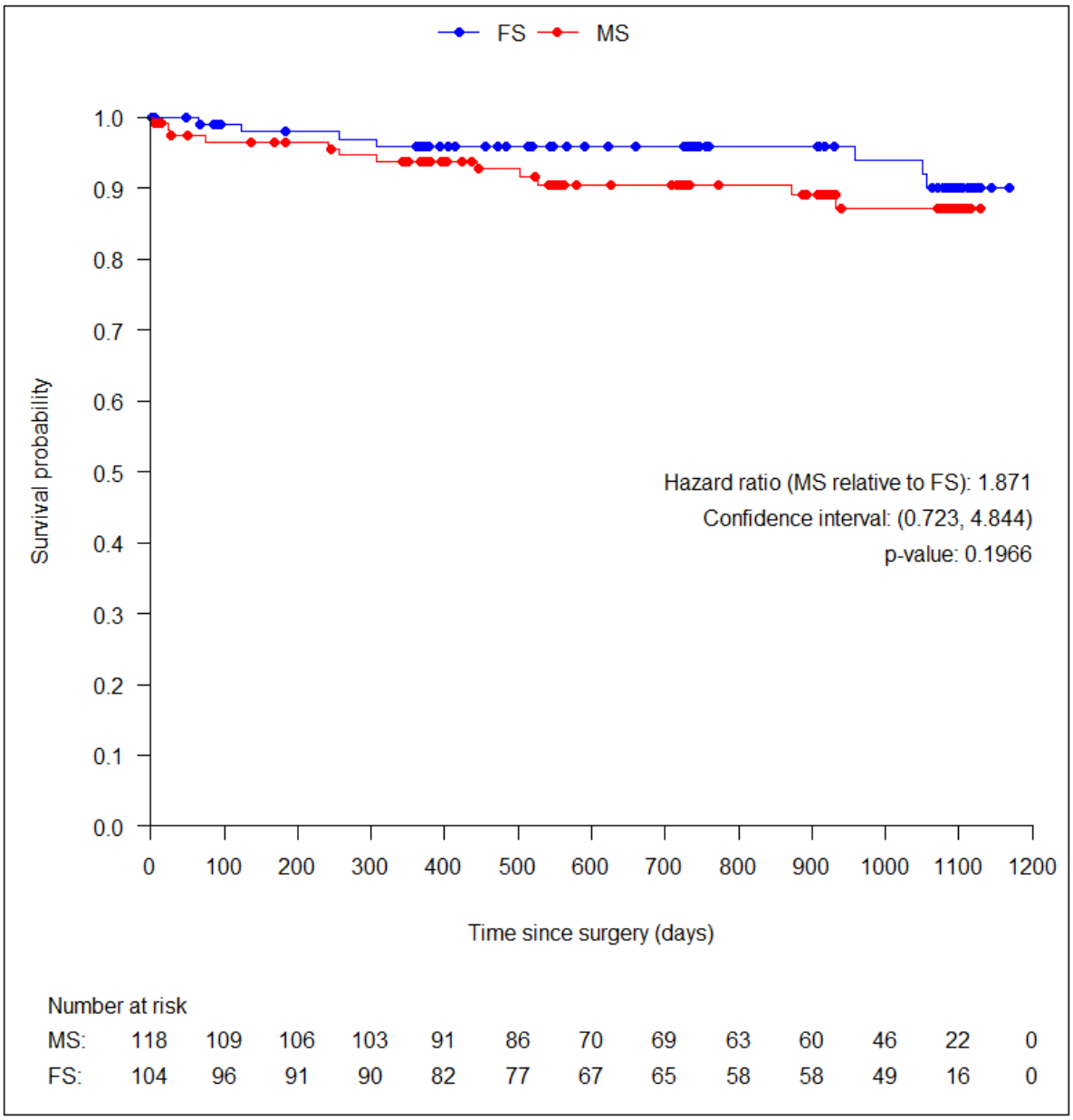
In total, 4 MS recipients and 13 FS recipients suffered wound infections within a year of surgery (one FS recipient suffered two infections). No patients who received a mechanical valve suffered a wound infection. Odds of wound infection were explored via logistic regression (complete case analysis in the safety population, with fixed treatment and sex effects, and with a random surgeon effect). The odds of suffering at least one wound infection were estimated to be lower for MS recipients than for FS recipients (MS/FS odds ratio 0.312, confidence interval 0.097 to 1.005, p-value 0.0511). Only two infections were categorised as deep (1 MS, 1FS).

Table A15. All deaths

	Treatment received	Treatment allocated	Cause	Relationship to treatment	Days from surgery to death
Cardiorespiratory	FS	FS	Endocarditis and sepsis.	Possibly related	124
	FS	FS	Lung infection.	Unrelated	1050
	FS	FS	Respiratory failure, pneumonia, chronic lymphocytic leukaemia.	Unrelated	1057
	MS	MS	Cardiac arrest and pericardial tamponade 2 days after surgery. Heart failure and left anterior pneumothorax 3 days after surgery.	Possibly related	3
	MS	MS	Type 2 respiratory failure and shock, multi-organ failure.	Possibly related	24
	MS	MS	Post-op arrest on HDU on day of surgery. Heart failure 26 days after surgery.	Possibly related	26
	MS	MS	Lower respiratory tract infection. Type 2 respiratory failure. NSTEMI during hospital admission.	Unrelated	75
	MS	MS	Endocarditis, infected valve. Refused all treatment including antibiotics. Palliation only.	Possibly related	241
	MS	MS	Exacerbation of COPD.	Unrelated	307
	MS	MS	Ischaemic heart disease.	Unrelated	502
	MS	MS	Myocardial infarction.	Unrelated	933
Non-cardiorespiratory	FS	FS	Sepsis.	Unrelated	66
	FS	FS	Metastatic prostate cancer.	Unrelated	256
	FS	FS	B cell lymphoma.	Unrelated	308
	FS	FS	Embolus of left common femoral artery, advanced colorectal cancer, AS, CHF.	Unrelated	958
	MS	MS	Metastatic bladder cancer.	Unrelated	257
	MS	MS	Death due to malignant tumour of oesophagus	Unrelated	445
	MS	MS	Diffuse large B cell lymphoma.	Unrelated	527
	MS	MS	Spontaneous subdural haemorrhage.	Unrelated	873

Table A15 shows that none of the patients who died were considered to be crossovers from MS to FS. However, there were three deaths among patients who were allocated and received MS but who were returned to theatre for redo FS. These were the deaths, all categorised as cardiorespiratory in Table A15, which occurred at 3, 26 and 933 days after surgery.

Figure A4. Kaplan-Meier curves for time to death by any cause



Patients are grouped by the treatment allocated to them. Patients who had no fatal events recorded were censored at the last time they were known to be alive. Times of censoring are indicated by points on the curves.

Appendix B: Economic Evaluation

Introduction

This trial collected data on resource and health service use for each patient during their in-patient stay through to the end of follow-up at 1 year. The economic analysis compared the costs and quality of life impacts of full and mini-sternotomy and assessed the cost-effectiveness of mini-sternotomy as an alternative to full median sternotomy.

The methods section first presents the unit costs, resource use data and the methods used to aggregate resource use and utility data at a patient level. The methods used to document and impute missing data follow. The last part describes the construction of incremental cost-effectiveness ratios and representation of uncertainty.

Results are presented first for raw data (with and without imputation) for costs and QALYs separately, followed by estimations of costs and QALYs that account for baseline differences. The final section provides results of probabilistic and deterministic sensitivity analyses.

Methods

Unit costs

All resource use data collected formed part of the patient-specific case-report form. Trained research nurses extracted data for inpatient stays from individual patient records. Face-to-face interviews with patients, by research nurses, provided data for quality of life as well as health service use during follow-up.

Multiplying the unit costs by each unit of resource use and summing these resource costs across each patient's 12 month follow-up from date of operation enabled aggregation of total cost per patient. Table B1 provides the unit costs used, with source of data. Where possible, national estimates of unit prices were used (e.g. PSSRU 2015 [1], NHS Ref 2014-15 [2]) to increase generalisability.

All resources were used once by patients (e.g. a GP visit or specific test), with the exception of two capital items used during surgery; the horizontal saw and defibrillator handles, both acquired for mini-sternotomy. These costs were apportioned, using clinical opinion, to each patient assuming a lifespan of 20 years and that surgeons undertake a total of 255 mini-sternotomies over five years.

Table B1. Unit costs

Item	Source	Consultation time/Codes	Mean 2014/15	SD
GP Visits	PSSRU 2015. 10.8b	Per patient contact lasting 17.2 minutes	£65.00	£13.00
GP Home Visits	PSSRU 2015. 10.8b	Per patient contact lasting 11.7 minutes	£45.00	£9.00
Nurse (GP Practice) Visits	PSSRU 2015. 10.6	Per patient contact 15.5 minutes	£14.47	£2.89
Nurse (Specialist Community) Home Visits	PSSRU 2015. 10.4	Per patient contact 15.5 minutes	£19.38	£3.88
Physiotherapy (outpatient)	NHS Ref 2014-15	Code: WF01A	£16.13	£3.23
Occupational Therapy (outpatient)	NHS Ref 2014-15	Code: WF01A	£16.67	£3.33
Physiotherapy (inpatient)	PSSRU 2015. 13.1	Per patient contact lasting 20 minutes	£12.67	£2.53
Occupational Therapy (inpatient)	PSSRU 2015. 13.2	Per patient contact lasting 20 minutes	£12.67	£2.53
Physiotherapy (home)	PSSRU 2015. 8.4.1	Per patient contact lasting 20 minutes	£27.00	£5.40
Theatre use	Papworth estimate		£20.00	£4.00
Horizontal surgical saw	Papworth estimate	20 year life span and are used in 255 surgeries in every 5 years	£3,138.22	£3.1
Paediatric internal cardioversion paddles			£161.71	£0.2

Internal paddle handle			£670.00	£0.7
*Reprocessing cost of defibrillator paddles for each surgery**		Per patient	£2.40	£2.40
Single use saw blade for mini-sternotomy		Per patient	£15.80	£15.80
Single use saw blade for full sternotomy		Per patient	£48.00	£48.00
Adult Critical Care	NHS Ref 2014-15	Total/weighted average	£1,274.92	£583.33
Specialised Ward	NHS Ref 2014-15	Code: SD01A	£387.96	£77.59
General Ward	NHS Ref 2014-15	Code: SD03A	£103.01	£20.60
Rehabilitation	PSSRU (1.3) 2015		£158.57	£31.71
24 hour Blood Pressure Monitoring	Lovibond et al. 2011, [3]		£61.47	£12.29
Radiography (chest)	Auguste et al. 2011, [4]		£3.46	£0.69
Echo TTE	NHS Ref 2014-15	Simple Echocardiogram	£83.94	£16.79
Echo TOE	NHS Ref 2014-15	Complex Echocardiogram	£128.49	£25.70
Echo Stress	NHS Ref 2014-15	Complex Echocardiogram	£128.49	£25.70
24 hour ECG	NHS Ref 2014-15	Electrocardiogram Monitoring	£140.69	£28.14
12 hour ECG	NHS Ref 2014-15	Electrocardiogram Monitoring	£140.69	£28.14
Exercise Tolerance Test	NHS Ref 2014-15	Electrocardiogram Monitoring	£140.69	£28.14
MRI scan	NHS Ref 2014-15	Total/weighted average	£146.15	£56.64
Full Pulmonary Function Testing	NHS Ref 2014-15	Code: DZ52Z	£55.32	£11.06
Cardiac Rehabilitation	NHS Ref 2014-15	Code: VC38Z	£97.84	£19.57
Cardio Clinic	NHS Ref 2014-15	Code: WF01A	£123.02	£24.60
Pacemaker	NHS Ref 2014-15	Code: EY08E	£76.32	£15.26
Blood tests	NHS Ref 2014-15	Code: DAPS08	£3.46	£0.69
Arrhythmia clinic	NHS Ref 2014-15	Total/weighted average	£131.14	£26.23
Wound clinic	NHS Ref 2014-15	Code: N25AF/AN	£54.93	£10.99
A&E visit	NHS Ref 2014-15	Total/weighted average	£140.59	£141.05
Computerised Tomography Scan	NHS Ref 2014-15	Total/weighted average	£122.31	£48.86

***** The lead clinician confirmed that: defibrillator is not routinely used and that the cost of paddles should apply to 30% of patients; and the cost of external defibrillator plates should be excluded for mini-sternotomy as the plate is only used when it is not possible to insert the paddles.

Patient-level aggregation of cost

This section describes the aggregation of costs, by patient, for the inpatient stay, post-discharge follow-up to 12 months and drug use.

Hospital stay: The time in the hospital from randomisation to discharge was disaggregated into theatre time, critical care unit (CCU) stay and cardiac ward stay as shown in Table B2. The total length of stay comprised time spent in surgery (measured in minutes), CCU (measured in hours) and cardiac ward (measured in days). Theatre time included duration of re-operations where applicable (a few patients had up to two returns to theatre) and corresponding CCU stays were added to the CCU hours. The total stay in the hospital, calculated using theatre time, critical care and ward stay, was compared with direct calculation of duration using date of operation and date of discharge to validate the breakdown of patient stay. After discharge from hospital, the majority of patients were discharged home but some were referred on to acute hospitals or rehabilitation centres (short or long term) for more care, and the costs of this additional stay were included.

Post-discharge: Resource use after discharge and up to twelve months post randomisation was collected at 6 week, 6 month and 12 month follow-up visits, with resource use divided into three categories: hospital admissions, tests and healthcare visits. A total of 28 different healthcare resources were used and aggregated over the follow-up period. For example, if a patient reported 1 blood test in discharge to 6 week follow-up period, 2 blood tests between 6 week to 6 month period and none after that, resource use was costed as £10.38 (3*£3.46) post discharge .

Table B2. Summary of resource use (without imputation)

		Full Sternotomy			Mini-sternotomy		
Primary Admission Costs	**Unit of measurement**	**Obs**	**Mean resource use/patient**	**SD**	**Obs**	**Mean resource use/patient**	**SD**
Theatre	Minutes	104	191.19	62.15	118	221.11	102.65
Critical care (ITU)	Hours	103	34.67	57.17	118	55.24	94.69
Cardiac ward	Days	103	7.09	4.31	118	6.90	3.87
Rehabilitation*	Days	103	2.45	11.90	117	1.68	10.27
Acute hospital*	Days	103	0.90	4.97	117	0.74	5.09
Physiotherapy (inpatient)	Days	103	5.90	4.21	117	5.90	5.16
Occupational therapy (inpatient)	Days	103	0.17	0.58	118	0.24	0.69
Follow-up (post discharge)							
ITU	Days	81	0.00	0.00	94	0.03	0.31
General ward	Days	92	2.87	14.37	101	0.86	3.43
Cardiac ward	Days	92	0.40	1.49	100	1.15	4.32
24 hour BP Monitoring	No. of tests	80	0.16	0.56	94	0.19	1.26
Radiography (chest)	No. of tests	80	0.49	0.89	94	0.64	0.90
Computerised Tomography Scan	No. of tests	80	0.14	0.52	94	0.15	0.51
Echo TTE	No. of tests	80	0.41	0.69	94	0.55	0.84
Echo TOE	No. of tests	80	0.03	0.22	92	0.03	0.18
Echo Stress	No. of tests	80	0.01	0.11	93	0.01	0.10
24 hour ECG	No. of tests	80	0.11	0.39	94	0.15	0.46
12 hour ECG	No. of tests	80	0.69	0.91	94	0.90	1.18
Exercise Tolerance Test	No. of tests	80	0.08	0.27	93	0.06	0.25
MRI scan	No. of tests	79	0.03	0.16	94	0.05	0.23
Full Pulmonary Function Testing	No. of tests	80	0.05	0.22	94	0.03	0.18
Blood test	No. of tests	81	0.05	0.22	94	0.06	0.35
A&E visit	No. of visits	80	0.09	0.28	94	0.22	0.51
Arrhythmia clinic	No. of visits	80	0.03	0.16	94	0.00	0.00
Cardiac Rehabilitation	No. of visits	79	0.84	2.76	93	0.32	1.43
Cardio Clinic	No. of visits	79	0.48	0.68	94	0.49	0.73
GP Home Visits	No. of visits	79	0.23	0.64	94	0.30	0.75
GP Visits	No. of visits	80	2.00	2.34	94	2.20	2.31
Nurse (Specialist Community) Home Visits	No. of visits	80	0.31	1.12	94	0.39	1.18
Nurse (GP Practice) Visits	No. of visits	80	2.10	10.02	92	0.75	1.46
Occupational therapy (outpatient)	No. of visits	80	0.11	0.71	94	0.06	0.62
Pacemaker	No. of visits	79	0.08	0.68	93	0.06	0.38
Physiotherapy (home)	No. of visits	80	0.05	0.35	94	0.00	0.00
Physiotherapy (outpatient)	No. of visits	80	0.04	0.19	94	0.01	0.10
Wound clinic	No. of visits	80	0.06	0.29	94	0.02	0.15
*discharged to convalescence/long term care/acute hospital instead of home							

Drugs: Drug use was matched to a corresponding unit cost using the NHS Electronic Drug tariff [5] and BNF [6] to sum costs across drug type for each patient.

Information on drugs administered during the primary admission was complete, with total amount of each drug per patient checked against patient prescriptions. However drug use post-discharge was self-reported and it was not possible to verify or retrieve any further data on this over the follow-up period.

Health State Utilities: This data was collected using EQ-5D-3L and SF-36 questionnaires. EQ-5D-3L responses were converted to utility values using Dolan et al (1995) [7] and to quality-adjusted life years (QALYs) for the trial period using the area under the curve method. SF-36 data was mapped to SF-6D utility values based on the ScHARR (School of Health and Related Research, University of Sheffield) algorithm and were converted to QALY scores (Brazier et al 2002 [8]). A value of 0 was assigned from date of death.

Missing data

The patterns of missing data for resource use and utilities were tested using Pearson Chi square goodness of fit and Wilcoxon rank sum tests for being missing at random and completely at random using the following variables: age, sex, treatment and health status at baseline (EQ-5D). The baseline characteristics assessed were not statistically significantly different between the two groups and multiple imputations were used for economic analysis. Patients were assigned zero cost and zero utility value from point of death.

Hospital stay: For primary admission, there were a few item non-responses for resource use data but no censored data. Complete information was available on all respondents barring one participant who withdrew from the trial after operation.

Post-discharge: The frequency of missing data for resource use after discharge is provided in Table B3 for the two groups. Imputation models did not converge at month twelve and resource use was aggregated over time, i.e. imputation was carried out for the aggregate value for each item rather than at each time period. The proportion of missing values in the aggregated utility data ranged from 11% to 25% in resource use post discharge (Table B3).

Table B3. Missing follow-up resource use

Follow up Resource Use	Full Sternotomy	Mini-sternotomy	Total
6 weeks			
Missing	3	4	7
Lost to follow up	4	6	10
Dead	1	4	5
Observations	96	104	200
6 months			
Missing	2	5	7
Lost to follow up	8	9	17
Dead	2	6	8
Observations	92	98	190
12 months			
Missing	9	4	13
Lost to follow up	11	13	24
Dead	4	7	11
Observations	80	94	174
Total	104	118	222

Drugs: Only drugs taken from randomisation to 12 month follow up period were accounted for (covering 3,078 drug uses of 118 different drugs). A number of assumptions (about quantity/dose and length of administration) were used to minimise the degree of missing information on drugs used. For example, when dosage or

frequency of dose per day was missing, the mode usage among trial participants was used or, if not available, the BNF dosage was used. Duration of medicinal use was calculated using start and stop dates for drugs used in primary admission and follow-up. However, when start/stop dates were missing, replies to a "yes/no" question on use of drugs at follow-up time points informed duration. For example if a drug was taken during inpatient stay, 6 week, 6 month and 12 month follow up, the drug was said to be used for entire 12 month trial period. However further assumptions about duration of medication were used when data was less forthcoming; for example drugs which were being taken only at 12 month follow up, without start date or stop date specified, were assumed to have been taken according to prescription every day for an average of three months (based on expert consultation). 58 records had insufficient information on usage for such personalised manual imputation, requiring predictive mean matching (conditioned on patient ID and name of drug).

Health State Utilities: EQ-5D-3L and SF-6D utility data were imputed at each follow-up as presented in Table B4, and percent of missing value ranged from 9% to 23%. Further breakdown of missing data for resource use and HRQoL questionnaires, and imputation required for each variable is provided in Table B4.

Table B4. Incomplete data and imputation

	Full Sternotomy				Mini-sternotomy			
Resource Use	**Complete**	**Incomplete**	**Imputed**	**Total**	**Complete**	**Incomplete**	**Imputed**	**Total**
Primary admission								
Theatre time (minutes)	104	0	0	104	118	0	0	118
Critical care stay (hours)	103	1	1	104	118	0	0	118
Cardiac ward stay (days)	103	1	1	104	118	0	0	118
Rehabilitation days*	103	1	1	104	117	1	1	118
Acute hospital days*	103	1	1	104	117	1	1	118
Physiotherapy visits	103	1	1	104	117	1	1	118
Occupational therapy visits	103	1	1	104	118	0	0	118
Follow-up (post discharge)								
Post discharge ITU days	81	23	23	104	94	24	24	118
Post discharge general ward stay	92	12	12	104	101	17	17	118
Post discharge cardiac ward stay	92	12	12	104	100	18	18	118
24 hour BP Monitoring	80	24	24	104	94	24	24	118
Radiography (chest)	80	24	24	104	94	24	24	118
Computerised Tomography Scan	80	24	24	104	94	24	24	118
Echo TTE	80	24	24	104	94	24	24	118
Echo TOE	80	24	24	104	92	26	26	118
Echo Stress	80	24	24	104	93	25	25	118
24 hour ECG	80	24	24	104	94	24	24	118
12 hour ECG	80	24	24	104	94	24	24	118
Exercise Tolerance Test	80	24	24	104	93	25	25	118
MRI scan	79	25	25	104	94	24	24	118
Pulmonary Function Testing	80	24	24	104	94	24	24	118
Blood test	81	23	23	104	94	24	24	118
A&E visit	80	24	24	104	94	24	24	118
Arrhythmia clinic	80	24	24	104	94	24	24	118
Cardiac Rehabilitation	79	25	25	104	93	25	25	118
Cardio Clinic	79	25	25	104	94	24	24	118
GP Home Visits	79	25	25	104	94	24	24	118

GP Visits	80	24	24	104	94	24	24	118
Nurse (Specialist Community) Home Visits	80	24	24	104	94	24	24	118
Nurse (GP Practice) Visits	80	24	24	104	92	26	26	118
Occupational therapy	80	24	24	104	94	24	24	118
Pacemaker	79	25	25	104	93	25	25	118
Physiotherapy (home)	80	24	24	104	94	24	24	118
Physiotherapy	80	24	24	104	94	24	24	118
Wound clinic	80	24	24	104	94	24	24	118
EQ-5D Score								
Baseline	95	9	9	104	105	13	13	118
4 Days Post Operation	89	15	15	104	92	26	26	118
Discharge	88	16	16	104	103	15	15	118
6 weeks follow-up	88	16	16	104	106	12	12	118
6 months follow-up	95	9	9	104	105	13	13	118
12 months follow-up	84	20	20	104	103	15	15	118
SF-6D Score								
Baseline	89	15	15	104	101	17	17	118
6 weeks follow-up	88	16	16	104	102	16	16	118
6 months follow-up	90	14	14	104	102	16	16	118
12 months follow-up	82	22	22	104	91	27	27	118

Imputation

Missing values were imputed conditional on sex, age, type of replacement valve used, risk classification measured using New York Heart Association (NYHA) Functional Classification and Canadian Cardiovascular Society (CCS) grading of angina. To avoid loss in efficiency, missing values for resource use and utility values at different time points were replaced using multiple imputations by chained equations.

Chained predictive mean matching was used to replace missing data for resource use and quality of life variables, and a total of 20 imputed datasets were created, stratified by treatment group. The imputed resource use is summarised in Table B5. However while conducting probabilistic analysis using bootstrap method; multiple imputation was carried out only once for each iteration with a total of 1000 iterations to adequately retain between imputation variance. The distribution of imputed values was visually checked for comparability with the observed data.

Table B5. Summary of resource use

		Full Sternotomy			Mini-sternotomy		
Primary Admission Costs	**Unit of measurement**	**Obs**	**Mean resource use/ patient**	**SD**	**Obs**	**Mean resource use/ patient**	**SD**
Theatre	Minutes	104	191.19	62.15	118	221.11	102.65
Critical care (ITU)	Hours	104	34.52	56.91	118	55.24	94.69
Cardiac ward	Days	104	7.07	4.29	118	6.90	3.87
Rehabilitation*	Days	104	2.42	11.84	118	1.66	10.22
Acute hospital*	Days	104	0.89	4.95	118	0.77	5.08
Physiotherapy (inpatient)	Days	104	5.88	4.20	118	5.94	5.15
Occupational therapy (inpatient)	Days	104	0.17	0.58	118	0.24	0.69

Follow-up (post discharge)							
ITU	Days	104	0.00	0.00	118	0.03	0.28
General ward	Days	104	2.61	13.55	118	0.77	3.20
Cardiac ward	Days	104	0.38	1.43	118	1.19	4.14
24 hour BP Monitoring	No. tests	104	0.18	0.52	118	0.17	1.13
Radiography (chest)	No. tests	104	0.55	0.87	118	0.61	0.83
CT Scan	No. tests	104	0.16	0.48	118	0.16	0.49
Echo TTE	No. tests	104	0.42	0.66	118	0.56	0.79
Echo TOE	No. tests	104	0.02	0.20	118	0.05	0.19
Echo Stress	No. tests	104	0.01	0.10	118	0.01	0.09
24 hour ECG	No. tests	104	0.13	0.41	118	0.16	0.44
12 hour ECG	No. tests	104	0.72	0.85	118	0.94	1.17
Exercise Tolerance Test	No. tests	104	0.07	0.24	118	0.06	0.23
MRI scan	No. tests	104	0.02	0.15	118	0.06	0.22
Full Pulmonary Function Testing	No. tests	104	0.06	0.22	118	0.03	0.16
Blood test	No. tests	104	0.06	0.21	118	0.07	0.33
A&E visit	No. visits	104	0.13	0.31	118	0.24	0.50
Arrhythmia clinic	No. visits	104	0.02	0.14	118	0.00	0.00
Cardiac Rehabilitation	No. visits	104	1.07	2.78	118	0.34	1.36
Cardio Clinic	No. visits	104	0.47	0.62	118	0.52	0.72
GP Home Visits	No. visits	104	0.27	0.64	118	0.25	0.68
GP Visits	No. visits	104	2.00	2.16	118	2.17	2.18
Nurse (Specialist Community) Home Visits	No. visits	104	0.38	1.06	118	0.47	1.22
Nurse (GP Practice) Visits	No. visits	104	1.93	8.83	118	0.71	1.32
Occupational therapy	No. visits	104	0.15	0.70	118	0.05	0.55
Pacemaker	No. visits	104	0.06	0.59	118	0.08	0.39
Physiotherapy (home)	No. visits	104	0.05	0.32	118	0.00	0.00
Physiotherapy	No. visits	104	0.05	0.20	118	0.02	0.11
Wound clinic	No. visits	104	0.06	0.28	118	0.03	0.15
*discharged to convalescence/long term care/acute hospital instead of home							

Adjustment method

To account for differences in baseline utility values, as well as skewness, censoring and confounding in cost data, linear regression models were used to provide adjusted estimates of mean values. Control variables used were age, sex, valve, EQ-5D-3L baseline value and treatment arm. The type of valve used for replacement was also controlled for, because it was used as a stratification factor in the randomisation.

Incremental cost effectiveness analysis and sensitivity analyses

Differences in estimated costs and EQ-5D QALYs between trial arms, using raw data with imputation, were tested using two-sample t-test with equal variances.

Incremental cost-effectiveness ratios were also constructed using adjusted mean estimates of costs and QALYs using 'seemingly unrelated regression', to account for correlation between costs and effects at the patient-level. This regression technique relies on the multivariate normality of the group-specific mean costs and QALYs, and is valid where the individual costs and QALYs are skewed (Faria et al 2014, [9]).

Probabilistic Sensitivity Analysis (PSA) was used to characterise the uncertainty of input parameters and a bootstrap approach (with 1000 bootstrapped samples) was applied to estimate the precision of results. The probability that mini-sternotomy is cost-effective when compared to full sternotomy is presented, at varying willingness to pay (WTP) threshold values, using a Cost Effectiveness Acceptability Curve (CEAC) and incremental net monetary benefit.

Deterministic sensitivity analyses and scenario analysis were used to explore the robustness of cost-effectiveness results that adopted different methodological approaches or assumptions (see Table B6). Baseline characteristics were assessed using Chi square and rank sum test, to assess whether patients included in the complete case analysis were different from those outside the complete case analysis.

Table B6. Summary of deterministic sensitivity and scenario analyses undertaken

Sensitivity analyses	Rationale
1. Complete case analysis	Only including respondents with no missing values across all variables and across follow-up; to check results in sample requiring no missing value imputation
2. Excluding patients who died during primary admission	Patients who died during primary admission were the main cost driver and required substantial surgical time and cardiac care; to assess whether excluding these patients would change recommendations.
3. Excluding additional equipment cost required	Assuming the additional equipment required for the surgeries already exists in the trusts;
4. Excluding follow-up resource use	To test the assumption that the cost difference between the two arms were accrued during primary admission, to allow comparison with literature that missed these costs, but still retain benefits as captured in other studies.
5. Excluding follow-up resource use and utility data	Data up to discharge had few missing values; also to assess impact of having a shorter cut-off time point for trial (as wider literature had) but provide a less biased analysis that measures benefits but not costs.
6. Use SF-6D utility values	SF-6D values used as an alternative construction for QALYs

Results

The comparison of mean costs per patient up to one year (see Table B7), using raw data with imputation, shows that mini-sternotomy was £1,714 more than median sternotomy although this was not statistically significant. The higher costs resulted from longer surgery time, additional equipment and longer time in critical care. EQ-5D QALYs were very slightly higher in the mini-sternotomy arm compared with full sternotomy (difference 0.0279), but this was not statistically significantly so (see Table B8), and there was no statistically significant difference in SF6D QALYs either. Figures B1 and B2 illustrate the distribution of total costs and QALYs across the patients in the trial.

Table B9 summarises the comparison of costs and QALYs. The additional cost of gaining an additional QALY using mini-sternotomy rather than median sternotomy when imputed using PMM method is £61,379 and the net monetary loss at a willingness to pay (WTP) of £20,000 is £1,155.

Seemingly unrelated regression analysis of costs and QALYs, adjusted for baseline characteristics showed that, in terms of QALYS, mini-sternotomy was not statistically significantly different from full sternotomy. Table B10 also shows that the coefficient for cost was positive, indicating mini-sternotomy was more costly than full sternotomy and that this difference was statistically significant. Mini-sternotomy is therefore dominated by median sternotomy. The cost effectiveness plane for the analysis is illustrated in Figure B3.

The probabilistic sensitivity analysis shows (see Figure B4) that, at a WTP per QALY of £20,000, there is a 3.7% likelihood that mini-sternotomy is cost-effective compared with median sternotomy and that this likelihood rises to 5.1% at a WTP of £30,000/QALY. The net monetary benefit of mini-sternotomy is negative across all WTP threshold values (Figure B5).

Deterministic sensitivity analyses (see Table B11) showed that mini-sternotomy was either dominated or had a huge ICER. The one exception to this was the complete case analysis (CCA-cost-effectiveness), which found mini-sternotomy to be cost-effective. The intervention cost less but also had slightly worse outcomes in this sample size, which was limited to only 90 cases. The result indicates a saving of £10,000 for a loss of one QALY. The sample is not representative of those with missing data and consisted a larger proportion of females than the sample outside the CCA-cost-effectiveness sample. The sensitivity analyses conducted using PSA (Table B12) consistently found full sternotomy to be a superior intervention to mini-sternotomy. The cost effectiveness planes for the sensitivity analyses are illustrated in Figure B6.

Table B7: Comparison of mean costs (SD) per patient up to 12 months post-randomisation (with imputation) (UK pounds, 2015)

		Full Sternotomy			Mini-sternotomy		
	Mean Unit cost	Obs	Mean cost/ patient	SD	Obs	Mean cost/ patient	SD
Primary Admission Costs							
Additional surgical items							
Horizontal surgical saw	£3,138.2	104	£0.0	£0.0	118	£3.1	£0.0
Single use saw blade for mini-sternotomy	£48.0	104	£0.0	£0.0	118	£48.0	£0.0
Single use saw blade for full sternotomy	£15.8	104	£15.8	£0.0	118	£0.0	£0.0
Paediatric internal cardioversion paddles	£161.7	104	£0.0	£0.0	118	£0.2	£0.0
Reprocessing cost of defibrillator paddles for each surgery	£2.4	104	£2.4	£0.0	118	£2.4	£0.0
Internal paddle handle	£670.0	104	£0.0	£0.0	118	£0.7	£0.0
*Cost of additional surgical items***		104	£16.52	£0.0	118	£52.0	£0.0
Theatre	£20.0	104	£3,823.8	£1,243.0	118	£4,422.2	£2,053.0
Critical care (ITU)	£1,274.9	104	£1,833.8	£3,023.2	118	£2,934.2	£5,029.9
Cardiac ward	£388.0	104	£2,743.7	£1,664.0	118	£2,676.3	£1,499.9
Rehabilitation*	£158.6	104	£384.2	£1,877.6	118	£263.4	£1,621.3
Acute hospital*	£388.0	104	£346.9	£1,918.9	118	£297.5	£1,971.3
Physiotherapy (inpatient)	£12.7	104	£74.5	£53.2	118	£75.2	£65.3
Occupational therapy (inpatient)	£12.7	104	£2.1	£7.3	118	£3.0	£8.7
Subtotal (primary admission)	**-**	**104**	**£9225.7**	**£6510.8**	**118**	**£10723.9**	**£8850.2**
Post Primary Admission Costs							
Hospital Admission							
ITU	£1,274.9	104	£0.0	£0.0	118	£32.4	£352.1
General ward	£103.0	104	£268.4	£1,395.4	118	£79.4	£329.5
Cardiac ward	£388.0	104	£149.2	£554.8	118	£463.6	£1,606.4
Tests							
24 hour Blood Pressure Monitoring	£61.5	104	£10.9	£32.0	118	£10.2	£69.5
Radiography (chest)	£3.5	104	£19.4	£30.9	118	£21.6	£29.5
Computerised Tomography Scan	£122.3	104	£19.4	£58.6	118	£19.7	£59.8
Echo TTE	£83.9	104	£35.1	£55.2	118	£46.9	£66.6
Echo TOE	£128.5	104	£2.5	£25.2	118	£6.5	£24.3
Echo Stress	£128.5	104	£1.2	£12.6	118	£1.1	£11.8
24 hour ECG	£140.7	104	£18.3	£57.2	118	£22.7	£62.3
12 hour ECG	£140.7	104	£101.5	£119.6	118	£132.9	£165.0
Exercise Tolerance Test	£140.7	104	£9.5	£34.0	118	£8.9	£32.6

MRI scan	£146.2	104	£3.5	£21.3	118	£9.3	£32.5
Full Pulmonary Function Testing	£55.3	104	£3.2	£12.4	118	£1.6	£9.1
Blood test	£3.5	104	£0.0	£0.1	118	£0.0	£0.1
Healthcare visits							
A&E visit	£140.6	104	£18.9	£43.0	118	£33.4	£70.4
Arrhythmia clinic	£131.1	104	£2.5	£18.1	118	£0.0	£0.0
Cardiac Rehabilitation	£97.8	104	£104.4	£271.9	118	£33.6	£133.4
Cardio Clinic	£123.0	104	£57.4	£76.3	118	£63.6	£88.1
GP Home Visits	£45.0	104	£12.1	£28.9	118	£11.3	£30.4
GP Visits	£65.0	104	£129.7	£140.6	118	£141.3	£141.8
Nurse (Specialist Community) Home Visits	£19.4	104	£7.3	£20.6	118	£9.0	£23.6
Nurse (GP Practice) Visits	£14.5	104	£28.0	£127.7	118	£10.3	£19.2
Occupational therapy (outpatient)	£16.7	104	£2.5	£11.7	118	£0.8	£9.2
Pacemaker	£76.3	104	£4.4	£44.9	118	£6.1	£29.5
Physiotherapy (home)	£27.0	104	£1.4	£8.6	118	£0.0	£0.0
Physiotherapy (outpatient)	£16.1	104	£0.8	£3.4	118	£0.3	£1.9
Wound clinic	£54.9	104	£3.4	£15.2	118	£1.6	£8.3
Subtotal (post-primary admission)	**-**	**104**	**£1014.9**	**£1777.5**	**118**	**£1168.2**	**£2077.9**
Drugs (total)	**-**	**104**	**£379.4**	**£548.2**	**118**	**£441.4**	**£976.7**
Total cost		**104**	**£10,620.0**	**£7,623.8**	**118**	**£12,333.5**	**£9,864.2**

*discharged to convalescence/long term care/acute hospital instead of home

**mean cost per patient estimated by assuming that the saw, paddle and handle have a twenty year life span and are used in 255 surgeries in every 5 years; NB: defib (paddle, handle and sterilisation cost) applicable in only 30% of cases

Table B8. Summary of utility values and QALYs

	Full Sternotomy			**Mini-sternotomy**		
EQ-5D	**Obs**	**Mean Utility**	**SD**	**Obs**	**Mean Utility**	**SD**
Baseline	104	0.6988	0.24	118	0.7793	0.18
4 Days Post Operation	104	0.3721	0.29	118	0.4430	0.28
Discharge	104	0.5815	0.23	118	0.5940	0.25
6 weeks follow-up	104	0.6930	0.21	118	0.7195	0.24
6 months follow-up	104	0.8272	0.22	118	0.8322	0.24
12 months follow-up	104	0.7584	0.29	118	0.8253	0.29
EQ-5D QALYs	104	0.7699	0.19	118	0.7978	0.21
	Full Sternotomy			**Mini-sternotomy**		
SF-6D	**Obs**	**Mean Utility**	**SD**	**Obs**	**Mean Utility**	**SD**
Baseline	104	0.6418	0.11	118	0.6802	0.12
6 weeks follow-up	104	0.6327	0.10	118	0.6356	0.14
6 months follow-up	104	0.7184	0.16	118	0.7332	0.19
12 months follow-up	104	0.6868	0.19	118	0.7058	0.23
SF-6D QALYs	104	0.6847	0.12	118	0.6989	0.16

Figure B1. Distribution of total cost

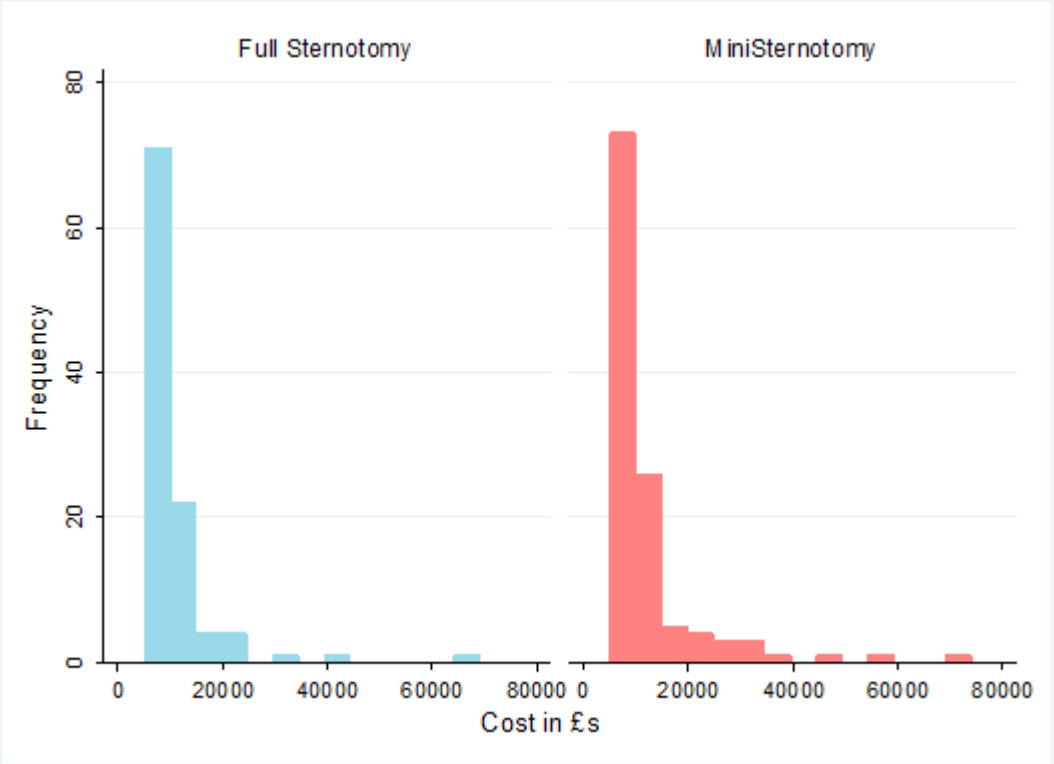


Figure B2. Distribution of QALYs

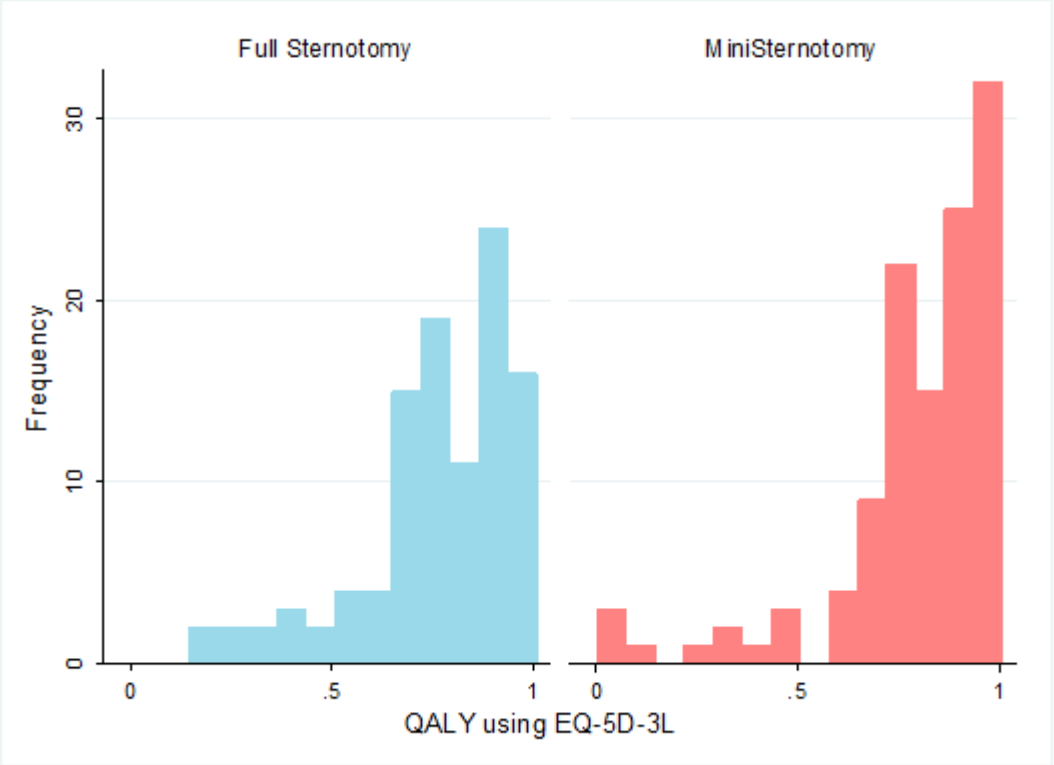


Table B9. Comparison of costs and QALYS (raw data, with imputation)

	Full Sternotomy (n=104)		Mini-sternotomy (n=114)	
	Mean	**SD**	**Mean**	**SD**
Total costs over 12 months	£10,620	£7,624	£12,334	£9,864
Incremental cost at 12 months (MS-FS)	-		£1,714	
Total EQ5D3L QALYs	0.7699	0.19	0.7978	0.21
Incremental EQ5D3L QALYs (MS-FS)	-		0.0279	
ICER	-		£61,379	
INMB at WTP of £20,000/QALY	-		-£1,155	
INMB at WTP of £30,000/QALY	-		-£876	

Table B10. Regression estimates of costs and QALYs

Dependant variable: EQ5D QALYs					
	Coefficient	**Std. Err.**	**P value**	**[95% Conf. Interval]**	
Mini-sternotomy	-0.0040	0.0245	0.87	-0.0520	0.0440
Male	0.0250	0.0246	0.31	-0.0231	0.0732
Age	-0.0051	0.0014	0.00	-0.0078	-0.0024
Baseline EQ-5D score	0.3037	0.0590	0.00	0.1880	0.4194
Tissue valve	0.0794	0.0459	0.08	-0.0107	0.1694
Constant	0.7391	0.1093	0.00	0.5249	0.9533
Dependant variable: Total Cost (£)					
	Coefficient	**Std. Err.**	**P value**	**[95% Conf. Interval]**	
Mini-sternotomy	2010.22	1201.57	0.09	-344.82	4365.25
Male	-1275.52	1205.23	0.29	-3637.73	1086.70
Age	98.32	67.58	0.15	-34.13	230.77
Baseline EQ-5D score	-983.50	2896.40	0.73	-6660.34	4693.33
Tissue valve	-853.43	2254.14	0.71	-5271.45	3564.60
Constant	5704.71	5362.01	0.29	-4804.64	16214.06

Table B11. Deterministic sensitivity analysis (using difference MS - FS, adjusted for baseline)

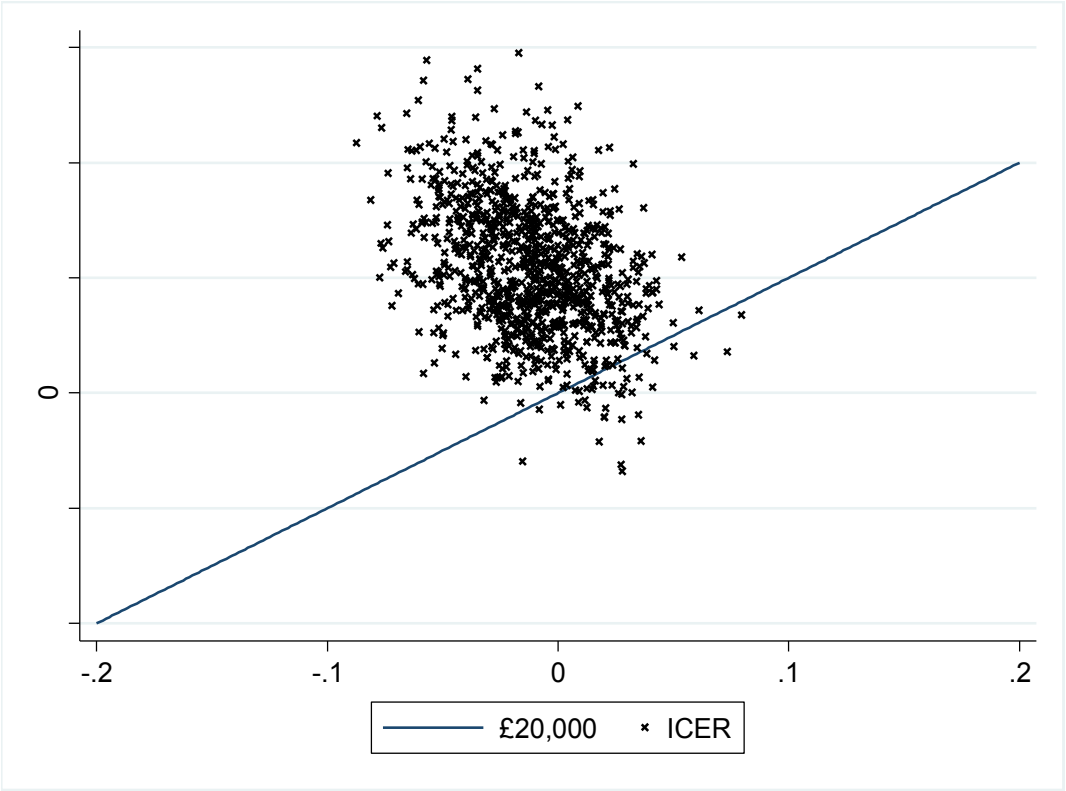
	Obs	Incremental cost over 12 months (MS-FS)		Incremental QALYs over 12 months (MS-FS)		ICER	INMB at £20,000 per QALY	INMB at £30,000 per QALY
		Mean	Std Error	Mean	Std Error			
Missing values imputed by PMM	222	£2,010	£1,202	-0.0040	0.0245	Dominated	-£2,089.26	-£2,128.78
Using SF6D QALYs	222	£2,010	£1,202	-0.0017	0.0178	Dominated	-£2,044.44	-£2,061.55
Assuming there is no additional equipment required for the two procedures	222	£1,975	£1,202	-0.0040	0.0245	Dominated	-£2,053.73	-£2,093.26
Excluding follow-up resource use	222	£1,664	£1,060	-0.0040	0.0245	Dominated	-£1,742.98	-£1,782.50
Complete case analysis	90	-£150	£661	-0.0145	0.0334	£10,333.62	-£139.89	-£284.60
Excluding patients who died during primary admission	219	£1,408	£1,128	0.0172	0.0216	£81,905.62	-£1,064.40	-£892.46
Including costs and QALY data only up to discharge	222	£1,664	£1,060	0.0013	0.0009	£1,316,409.02	-£1,638.66	-£1,626.02

Table B12. Probabilistic sensitivity analysis (using difference MS - FS, adjusted for baseline)

	Obs	Incremental cost over 12 months (MS-FS)		Incremental QALYs over 12 months (MS-FS)		ICER	INMB at £20000	INMB at £30000
		Mean	Std Error	Mean	Std Error			
Missing values imputed by PMM and adjusted	1000	£2,154	£36	-0.0122	0.0008	Dominated	-£2,396.99	-£2,518.59
Using SF6D QALYs	1000	£2,154	£36	-0.0075	0.0006	Dominated	-£2,303.03	-£2,377.66
Assuming there is no additional equipment required for the two procedures	1000	£2,245	£40	-0.0096	0.0008	Dominated	-£2,437.25	-£2,533.50
Excluding follow-up resource use	1000	£1,835	£35	-0.0131	0.0008	Dominated	-£2,096.58	-£2,227.15
Complete case analysis	1000	-£111	£22	-0.0121	0.0011	£9,170.78	-£130.56	-£251.12
Excluding patients who died during primary admission	1000	£1,433	£32	0.0147	0.0007	£97,425.25	-£1,138.55	-£991.50
Including costs and QALY data only up to discharge	1000	£1,835	£35	0.0008	0.0000	£2,415,384.92	-£1,820.25	-£1,812.65

Figure B3. Cost effectiveness plane (using difference MS-FS, adjusted for baseline)

B3.1 Using EQ-5D to estimate QALY



B3.2 Using SF-36 to estimate QALY

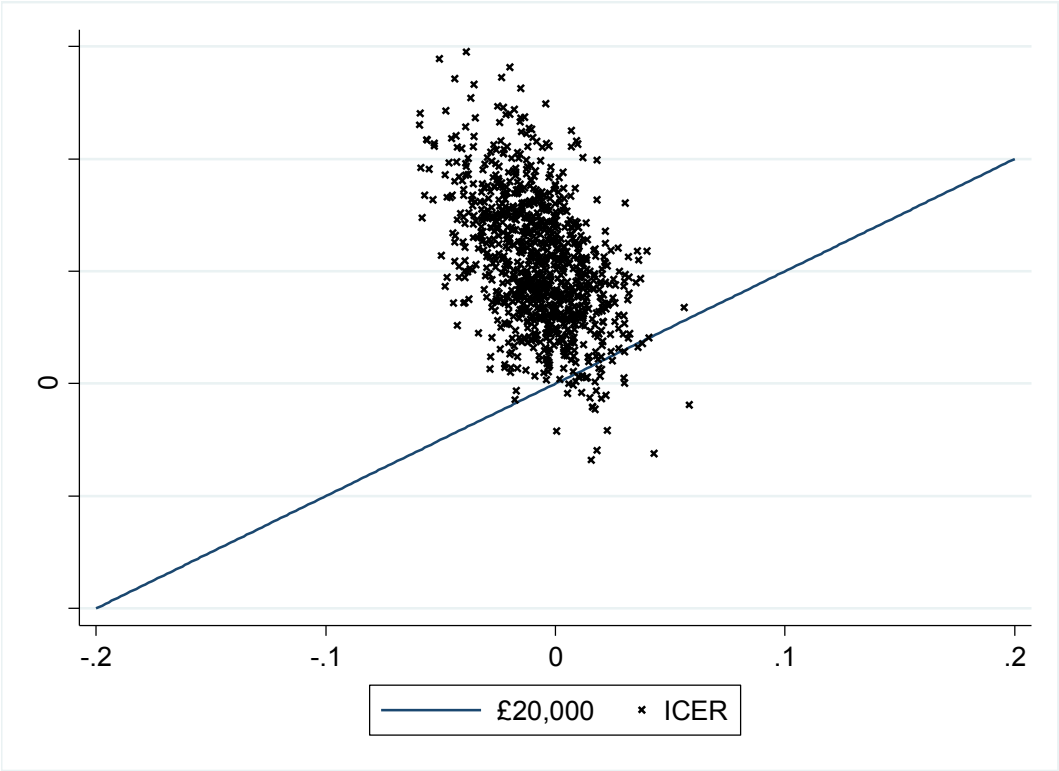


Figure B4. Cost-effectiveness acceptability curve (EQ-5D)

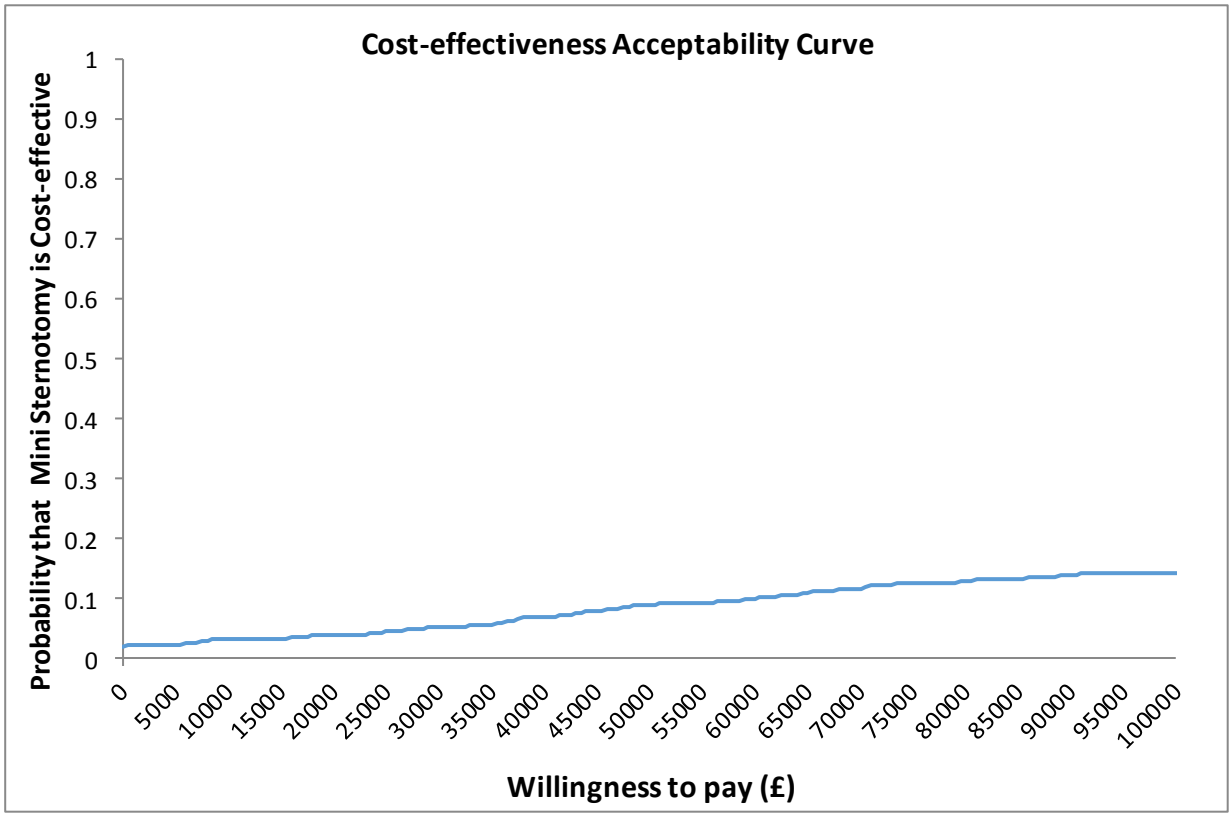


Figure B5. Net monetary benefit (controlling for baseline characteristics and missing data)

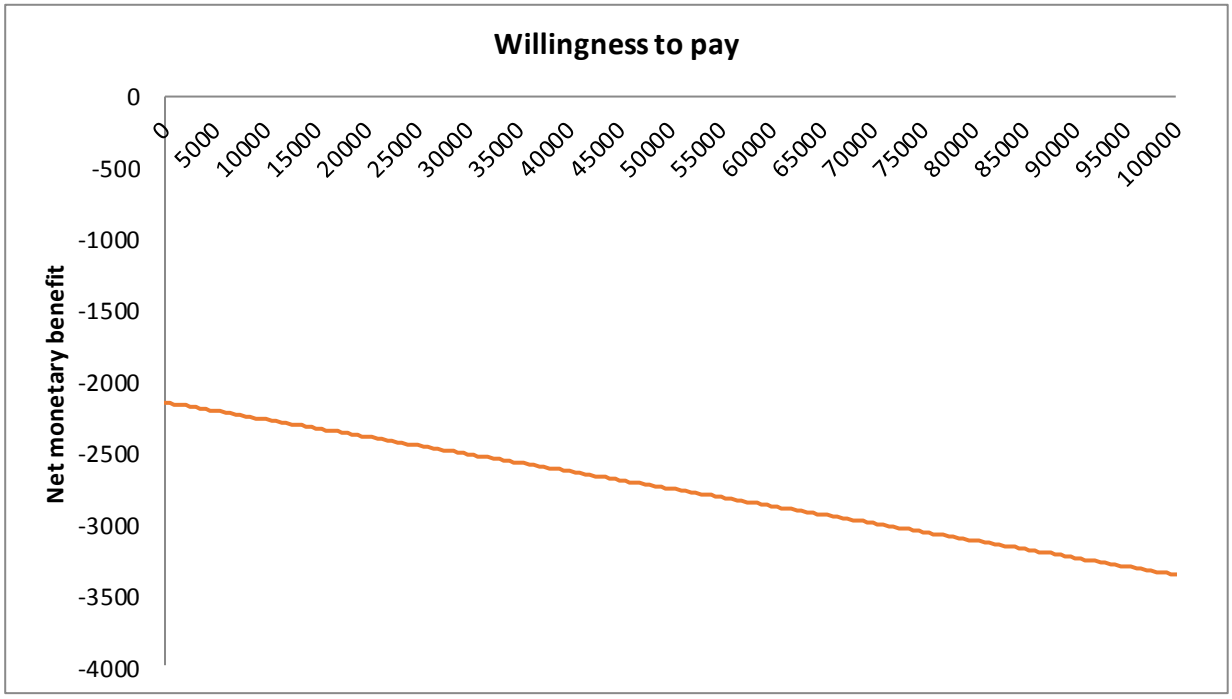
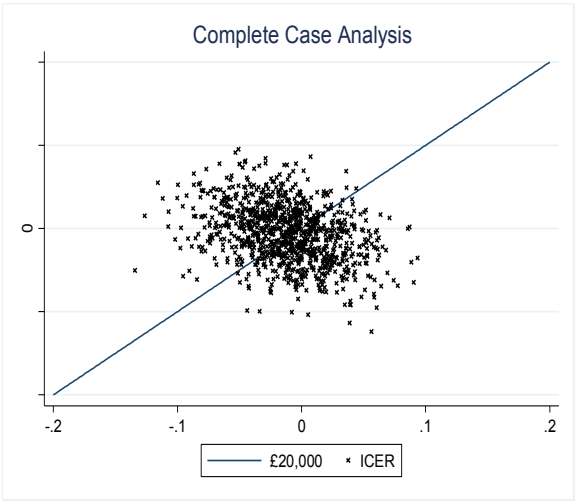
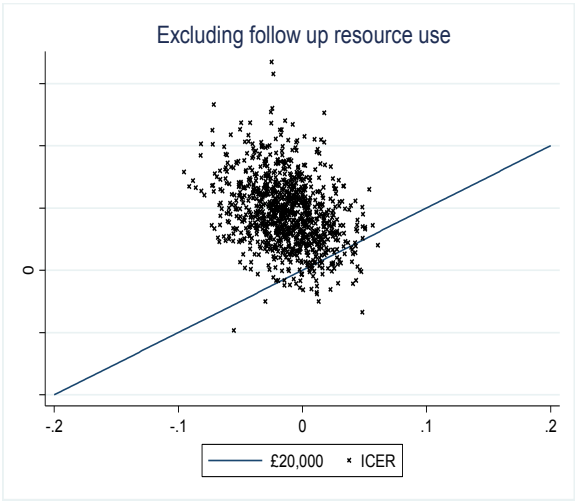
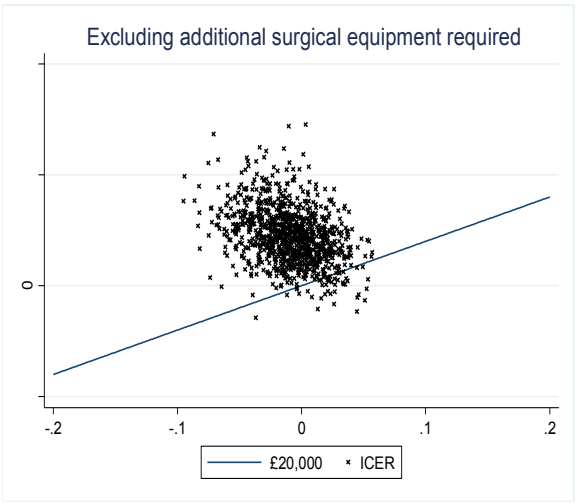
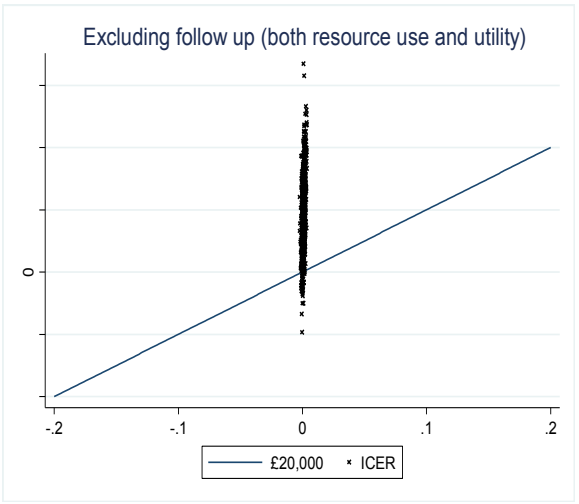


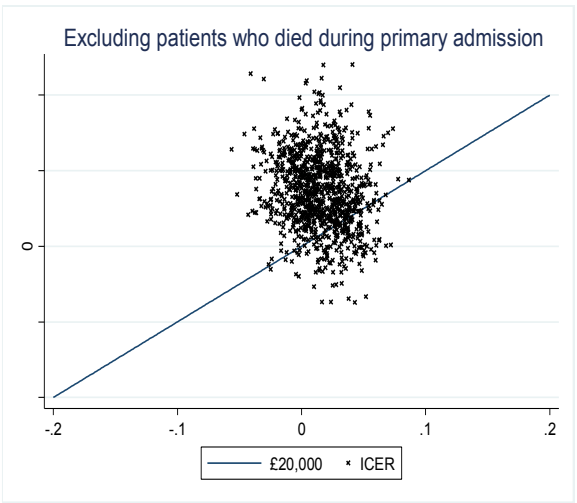
Figure B6. Sensitivity analyses using difference (MS - FS), adjusted for baseline











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	☐	☐	☐	☐	
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	☐	☐	☐	☐	

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JTCVS Form For Disclosure of Potential Conflicts of Interest

Section 4. Intellectual Property - Patents and Copyrights

Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

If yes, please fill out the appropriate information below.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
	☐	☐	☐	☐	
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JTCVS Form For Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Claire
2. Surname (Last Name): Matthews
3. Date: 17 April 2018

4. Are you the corresponding author? ☐ Yes ☑ No

5. Manuscript Title:
Mini-Stern Trial: A randomised trial comparing mini-sternotomy to full median sternotomy for aortic valve replacement

6. Manuscript Identifying Number (if you know it):
JTCVS-18-2

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Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
Royal Papworth Hospital NHSFT	☑	☐	☐	☐	NIHR Research for Patient Benefit Grant
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	

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Section 1. Identifying Information

1. Given Name (First Name): Catherine
2. Surname (Last Name): Sudarshan
3. Date: 18.04.2018

4. Are you the corresponding author? ☐ Yes ☑ No

5. Manuscript Title:
Mini-Stern Trial: A randomised trial comparing mini-sternotomy to full median sternotomy for aortic valve replacement

6. Manuscript Identifying Number (if you know it):
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Section 1. Identifying Information

1. Given Name (First Name): John
2. Surname (Last Name): Dunning
3. Date: 17th April 2018

4. Are you the corresponding author? ☐ Yes ☐ No

5. Manuscript Title:
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JTCVS Form For Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Jeshika
2. Surname (Last Name): Singh
3. Date: 17/04/2018

4. Are you the corresponding author? ☐ Yes ☑ No

5. Manuscript Title:
Mini-Stern Trial: A randomised trial comparing mini-sternotomy to full median sternotomy for aortic valve replacement

6. Manuscript Identifying Number (if you know it):
JTCVS-18-2

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	☐	☐	☐	☐	
	☐	☐	☐	☐	
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2. Surname (Last Name): Valchanov
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2. Surname (Last Name): Sharples
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	☐	☐	☐	☐	
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THE JOURNAL OF
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JTCVS Form For Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Narain
2. Surname (Last Name): Moorjani
3. Date: 17th Apr 2018

4. Are you the corresponding author? ☐ Yes ☑ No

5. Manuscript Title:
Mini-Stern Trial: A randomised trial comparing mini-sternotomy to full median sternotomy for aortic valve replacement

6. Manuscript Identifying Number (if you know it):
JTCVS-18-2

Section 2. The Work Under Consideration for Publication

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Do you have any patents, whether planned, pending or issued, broadly relevant to the work? ☐ Yes ☑ No

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JTCVS Form For Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Pedro
2. Surname (Last Name): Catarino
3. Date: 17/04/2018

4. Are you the corresponding author? ☐ Yes ☑ No

5. Manuscript Title:
Mini-Stern Trial: A randomised trial comparing mini-sternotomy to full median sternotomy for aortic valve replacement

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JTCVS Form For Disclosure of Potential Conflicts of Interest

Section 1. Identifying Information

1. Given Name (First Name): Sukumaran
2. Surname (Last Name): Nair
3. Date: 18th April 2018

4. Are you the corresponding author? ☑ Yes ☐ No

5. Manuscript Title:
Mini-Stern Trial: A randomised trial comparing mini-sternotomy to full median sternotomy for aortic valve

6. Manuscript Identifying Number (if you know it):
JTCVS-18-2

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Section 1. Identifying Information

1. Given Name (First Name): Thaseegaran
2. Surname (Last Name): Pillay
3. Date: 27/04/2018

4. Are you the corresponding author? ☐ Yes ☑ No

5. Manuscript Title:
Mini-Stern Trial: A randomised trial comparing mini-sternotomy to full median sternotomy for aortic valve replacement

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Section 1. Identifying Information

1. Given Name (First Name): Yasir
2. Surname (Last Name): Abu-Omar
3. Date: 18 April 2018

4. Are you the corresponding author? ☐ Yes ☑ No

5. Manuscript Title:
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If yes, please fill out the appropriate information below.

Name of Institution/Company	Grant?	Personal Fees?	Non-Financial Support?	Other?	Comments
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	☐	☐	☐	☐	
	☐	☐	☐	☐	
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JTCVS Form For Disclosure of Potential Conflicts of Interest

Instructions

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. The form is designed to be completed electronically and stored electronically. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in five parts.

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1. Identifying information.

2. The work under consideration for publication.

This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking "No" means that you did the work without receiving any financial support from any third party - that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check "Yes".

3. Relevant financial activities outside the submitted work.

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Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the **36 months** prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work's sponsor that are outside the submitted work should also be listed here. If there is a question, it is usually better to disclose a relationship than not to do so.

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Definitions

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Other: Anything not covered under the previous three boxes
Pending: The patent has been filed but not issued
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Royalties: Funds are coming in to you or your institution due to your patent

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Section 1. Identifying Information

1. Given Name (First Name): Benjamin
2. Surname (Last Name): Thorpe
3. Date: 17 April 2018

4. Are you the corresponding author? ☐ Yes ☑ No

5. Manuscript Title:
Mini-Stern Trial: A randomised trial comparing mini-sternotomy to full median sternotomy for aortic valve replacement

6. Manuscript Identifying Number (if you know it):
JTCVS-18-2

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	☐	☐	☐	☐	
	☐	☐	☐	☐	

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Required Information

Manuscript Title: Mini-Stern Trial: A randomised trial comparing mini-sternotomy to full median sternotomy for aortic valve replacement

Corresponding Author: Sukumaran K Nair

Authorship Responsibility and Contribution

Based on "A new standard for authorship" from The Council of Science Editors (http://tinyurl.com/lkab4jp).

By submitting this manuscript, each author certifies that:

They made a direct and substantial contribution to the work reported in the manuscript by participating in at least the following three areas:

- made substantial contributions to conception and design and/or acquisition of data and/or analysis and interpretation of data;
- participated in drafting and/or revising the paper and provided important intellectual contributions; and
- gave final approval of the submitted version and any revised versions submitted prior to acceptance.

They participated to a sufficient degree to take public responsibility for the work and believe that the manuscript describes truthful facts. They declare that they shall produce the data on which the manuscript is based for examination by the editors or their assignees, should it be requested. Each author also agrees to allow the corresponding author to make decisions regarding submission of the manuscript to the Journal, changes to galley proofs, and prepublication release of information in the manuscript to the media, federal agencies, or both.

In the table below, please designate the substantive contribution(s) of each author.

	Author Name	Conception and design	Analysis and interpretation	Writing the article	Critical revision of the article	Final approval of the article	Data Collection	Provision of materials, patients, or resources	Statistical expertise	Obtaining funding	Literature search	Administrative, technical, or logistic support
1.	Sukumaran K Nair	✔	✔	✔	✔	✔		✔		✔	✔	
2.	Catherine D Sudarshan AND Massimiliano Codispoti	✔			✔	✔		✔				
3.	Benjamin S Thorpe AND Linda Sharples		✔	✔	✔	✔	✔	✔	✔	✔	✔	
4.	Jeshika Singh AND Julia Fox-Rushby		✔	✔	✔	✔	✔	✔	✔	✔	✔	
5.	Carol J Freeman AND Claire Matthews			✔	✔	✔	✔	✔		✔	✔	✔
6.	Thasee Pillay				✔	✔		✔				
7.	John Dunning AND Yasir Abu-Omar				✔	✔		✔				
*8.	Pedro Catarino AND Massimiliano Codispoti				✔	✔		✔				
*9.	Narain Moorjani			✔	✔	✔		✔				
*10.	Kamen Valchanov				✔	✔		✔				

**If more than 7 authors are included in the manuscript, authors MUST provide an explanation in the next section for the Editor's review.*

Additional Author Explanation

The number of authors should be limited to those individuals who made direct contributions to the intellectual content of the paper. For most papers, 7 authors should be sufficient. Additional authors may be added if their inclusion can be justified and if each author is able to assume responsibility for the validity of the results and conclusions in the manuscript. **If more than 7 authors are included in the manuscript, authors MUST provide an explanation below for the Editor's review.**

This study was conducted in two surgical units in the UK involving 8 Surgeons, 1 Anaesthetist/Intensivist, 2 Health Economists, 2 Trial Managers and 2 Biostatisticians. Each co-author listed above have contributed significantly to the co-ordination and management of the trial, data collection, data analysis and preparation of the manuscript and hence included in the list of authors. Therefore I request the Editor to include all co-authors listed.

Statistical Collaboration Statement

Because data and their analyses often constitute the supporting evidence for inferences drawn from studies submitted to the Journal, the Editors remind authors that all manuscripts with statistical analyses undergo statistical review by the Journal. The review includes study design, analysis, interpretation, and reporting. The manuscripts are not published without an acceptable rating by the statistical editorial staff. Therefore, to minimize revision and delays, authors should request review of such manuscripts by a statistician prior to submission. This is best done by involving a statistician as a collaborator from the inception to completion of the study. Statisticians should have a master's or doctoral degree (or equivalent) in biostatistics or related field, and experience in the design, analysis and interpretation of biomedical data of the type used in this paper. The statistician, along with the authors, possess scientific responsibility for the analysis and interpretation of the data presented in the final version of this manuscript.

Did this manuscript require the performance of complex statistical methods? ☑ Yes ☐ No

If yes, please complete the information below regarding the statistical expert for this manuscript. **Be sure to include a short description of their area(s) of statistical expertise.**

Name: Professor Linda Sharples

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Email: Linda.Sharples@lshtm.ac.uk

Area(s) of Statistical Expertise:

Biomedical Statistics, Randomised Controlled Trials and Epidemiology.

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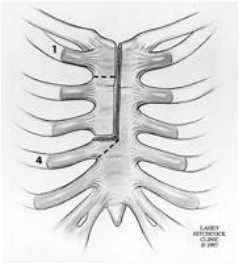
The MiniStern Trial – A Pragmatic, Prospective, Randomised, Controlled Trial Comparing Upper Mini Sternotomy to Full Median Sternotomy as a Surgical Approach for Aortic Valve Replacement



MiniStern

PROTOCOL

DATE 29 October 2013

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Protocol Identification Number: P01292
Protocol Version Number: 5

CONTENTS

1. TRIAL OVERVIEW

1.1. Background

Aortic valve replacement (AVR) is the second most common cardiac surgical procedure in the UK (3436 patients in 2006/07 [1]). As increasing numbers of patients are referred for AVR each year including a large proportion of older patients [9] operative strategies are required to hasten postoperative recovery without compromising surgical quality or patient satisfaction.

A multitude of preoperative variables may influence a surgeon's decision to modify the standard surgical approach toward less invasive strategies, but the primary determinant is likely to be the surgeon's level of experience with such procedures. A majority of AVR procedures are thus far still performed through a full median sternotomy [9].

The advantage of the full median sternotomy compared with less invasive techniques is that it affords more options for pump cannulation and myocardial preservation providing optimal access to the heart and major vessels. In general, full median sternotomy is well tolerated but, together with cardiopulmonary bypass, it is a potential contributor to complications in high-risk individuals and is commonly perceived with apprehension by patients and referring physicians [9].

Different techniques have been proposed to create safer and less invasive AVR procedures, including percutaneous AVR techniques which are still very experimental and carry a high level of risk [9]. Performance of AVR through smaller incisions is an alternative approach which provides considerable psychological comfort to patients and may confer additional benefits in terms of improved recovery and reduced activation of inflammatory cascades. Although actual results vary considerably among centres, the overall advantages of minimally invasive approaches have been reported to include less postoperative pain, improved cosmetics, less blood loss, fewer pulmonary and wound complications, and shorter length of stay [9].

An upper mini-sternotomy has the potential to hasten postoperative recovery following isolated AVR, resulting in reduced lengths of hospital stay and improved patient satisfaction [3, 4, 5, 6, 9]. In a recently published randomised controlled trial, 93% patients who had an AVR procedure via a mini-sternotomy approach reported only minimal post operative pain compared to 97% who reported severe pain following full median sternotomy [4].

The scientific validity of a majority of published comparisons of MiniStern to conventional AVR is poor. Most reports are from case series or non-randomised observational studies and none have been conducted in a UK NHS setting. Only four small RCTs comparing MiniStern to conventional AVR [3, 4, 7, 8] have been identified. The RCTs all had small sample sizes ranging from 40-80 participants and reported post operative outcomes varied considerably. For example, reductions in hospital stay using MiniStern ranged from 0-55%. The two largest published cohort studies [5,6] have suggested that hospital stay can be reduced by 16% and 25%, but these were observational studies.

Thus, there is no robust evidence on which to base guidelines for AVR surgical approaches in the UK.

1.2. Study Design

This proposed study is a pragmatic, prospective randomised controlled trial comparing upper mini-sternotomy (MiniStern) to full median sternotomy as a surgical approach to first time isolated aortic valve replacement (AVR).

1.3. Primary Outcome

The primary outcome will be total length of stay in hospital for the index AVR operation measured in days. Length of hospital stay has been chosen as the primary outcome because it can be easily measured and is a composite measure sensitive to the patient related outcomes we hope to improve by using mini-sternotomy – namely early mobilisation, reduced pain levels and reduced sternal wound complications. We believe that if a patient is fit for discharge then a reduced length of hospital stay is an important outcome for them in terms of morale, satisfaction with treatment and health related quality of life.

However we recognise that with a predominately older population, patients may have co morbidities and social factors that delay discharge so that length of stay is determined by these issues rather than by fitness for discharge. Although randomisation should ensure that such co morbidities and social factors are equally distributed between study groups, potential confounding variables will be carefully recorded.

1.4. Secondary Outcomes

1.4.1. Operative Data

These will be collected on the day of surgery and will include total theatre time, cross clamp time, cardiopulmonary bypass time, blood loss, blood transfusion, and skin to skin time.

1.4.2. In-Hospital Data

Fitness for discharge – Patients will be assessed independently by the multi-disciplinary discharge team and the research nurse according to a formal discharge protocol (Annex 1). The research nurse will record the postoperative day when the patient was fit to be discharged home and the final discharge date and destination.

Time to first mobilisation: defined as walking independently

Time to extubation: total number of hours of intubation (to account for re-intubation)

Time to mediastinal drain removal

Postoperative pain levels: the hospital's visual and numerical analogue scale to score pain will be administered daily until hospital discharge (Annex 2).

Need for analgesia: after extubation and when competent to self administer, all patients will have a patient controlled analgesia (PCA) pump of morphine Until this time they will receive a continuous infusion of morphine . They will also receive regular Paracetamol (1g qds till the date of discharge) to reflect hospital pain management protocols. The total dose of all pump delivered analgesia will be calculated prior to discharge. Any adjunct/supplementary analgesia will also be recorded. Morphine intolerance will also be recorded.

Wound infection and requirement for antibiotics. Wound exudate will be swabbed for microbiological culture as per hospital protocol Wound Infection will be assessed and defined according to the Health Protection Agency Protocol for the Surveillance of Surgical Site Infection version 4, July 2008 (Annex 4)

Perioperative bleeding and blood transfusion: Blood loss during the first 12 hours after surgery will be recorded. The blood transfusion requirement during the first 48 hours after surgery in all cases will be recorded. The threshold haemoglobin level below which blood transfusion will be triggered will be 8 g% or below, as per current hospital transfusion protocol. Haemoglobin will be measured as per current hospital transfusion protocol.

1.4.3. Health Related Quality Of Life and Patient Satisfaction after Surgery

Health related quality of life and patient satisfaction will be assessed at baseline, 6 weeks, 6 months and 12 months following surgery using the SF-36 [11], CROQ-CABG [12] and the EQ-5D [13] questionnaires.

The EQ-5D will also be repeated at day 4, on discharge and every 6 months after year one until the study is completed.

The CROQ-CABG questionnaire was designed for cardiac patients undergoing coronary artery bypass surgery and includes angina symptoms, reported impact of the heart condition on physical, psychosocial and cognitive functioning and pertinent post-operative sections on surgical chest wound and satisfaction with the heart operation. The only modification to the CROQ-CABG will be to remove questions related to arm and leg wounds that are specific to bypass grafting. The relatively large sample size of this study will allow us to validate the use of this modified questionnaire (CROQ-AVR) in AVR patients (Annex 3).

1.4.4. Clinical Outcomes

Heart function (LVEF) will be assessed by echocardiography at baseline, day of discharge and 6 months post surgery.

Respiratory function (FEV1) will be assessed by hand held spirometry at baseline; day of discharge; 6 weeks and 6 months.

1.5. Schedule of Events

Details	Pre Admission	Pre-op day /operation day	Day 1 post op	Daily checks	Day 4 post op	Day of discharge	6 weeks Routine	6 months Research	12 months Telephone
Patient screened and given PIS by surgeon	X	U							
Telephone follow up by Research Nurse	X								
Assessment of inclusion/exclusion criteria	X	U							
Informed consent	X	U							
HRQoL assessment SF-36, CROQ-AVR, EQ-5D (EQ-5D repeated 6 monthly to 36 months)	X	U			X (EQ-5D only)	X (EQ-5D only)	X	X	X
Spirometry	X	U				X	X	X	
Transthoracic Echocardiography	(X) Routine	(U) Routine				X		X	
Randomisation		X							
In hospital routine data collection		X	X	X	X	X			
Pain and analgesia assessment		X	X	X	X	X	X		
Wound and Antibiotic Assessment		X	X	X	X	X	X		
Fitness for discharge assessment (length of stay in ICU, Total hospital stay)				X	X	X			
Adverse Event assessment and reporting (up to 36 months)		X	X	X	X	X	X	X	X
Resource use data (up to 36 months)		X	X	X	X	X	X	X	X

X study procedure, (X) and (U) routine procedure, U study procedure for in-house urgent patients only

Study Population

1.6. Inclusion criteria

- Age > 18 years at the time of surgery
- Elective, first time, isolated Aortic Valve Replacement
- Documented severe emphysema or COPD if the FEV1 or TLCO is >40% predicted

1.7. Exclusion criteria

- Documented poor LV function or LVEF less than or equal to 30%
- Documented chest wall deformities
- Documented severe emphysema or COPD if the FEV1 or TLCO is <40% predicted
- Current BMI > 35
- Concomitant cardiac surgery
- Redo surgery
- Median sternotomy indicated (includes inability to have a transoesophageal echocardiogram).

1.8. Sample Size

- Sample size is based on an audit of 252 patients undergoing AVR at Papworth Hospital NHS Trust in 2007/08 who had a mean hospital stay of 11.7 days (SD 6.2). From 4 published RCTs [3, 4, 7, 8] and two large cohort studies [5, 6] we estimate that, using mini-sternotomy, a 20% reduction in total hospital stay from 11.7 to 9.36 days is plausible and clinically important.

- To detect this level of change with 80% power and 2 sided alpha of 5% we would need a sample size of 110 patients per group or 220 in total. For hospital stay it is unlikely that there will be loss to follow up.

1.9. Recruitment

At the surgical clinic the local investigator or an experienced delegated representative will identify patients who are eligible for the trial, will discuss participation in the trial with the patient and, if they are interested, will give the patients a copy of the patient information sheet to take home.

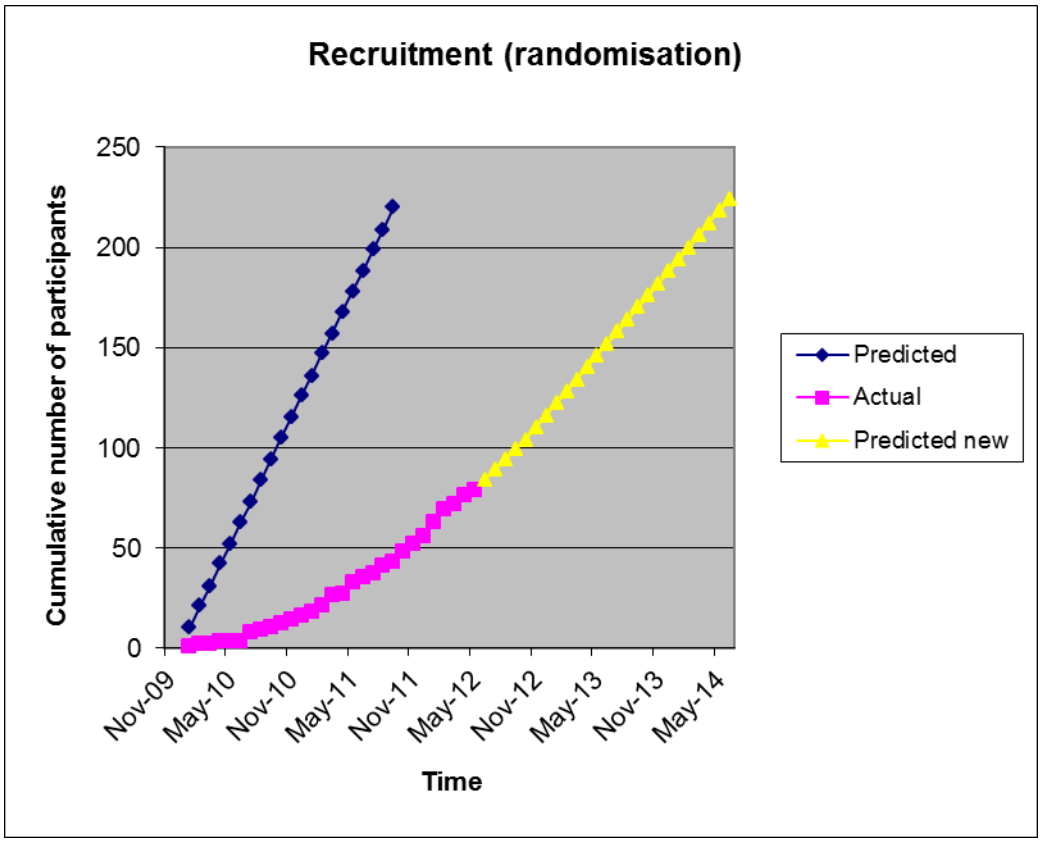
The research nurse will contact these patients at home by telephone to see if they are still interested in taking part and to talk about the study in more detail, answering any questions they may have.

Most patients awaiting surgery attend a routine surgical clinic 1-2 weeks before their scheduled admission. Patients will have the opportunity to discuss the study again at this visit. For those who would like to participate, the research nurse will confirm eligibility and obtain written informed consent. Once consent has been obtained baseline tests will be completed.

In-house urgent patients awaiting AVR after admission for other investigations will be approached by their surgeon or an experienced member of the research team who will introduce the study and give the patient a copy of the in-patient information sheet to read. The patient will have the opportunity to discuss the study with relatives and their care team. A member of the research team will later visit the patient on the ward to see if they are

interested in taking part and to talk about the study in more detail, answering any questions they may have. We will aim to give in-house urgent patients at least 24 hours to consider whether or not they would like to take part. For those who would like to participate, the research nurse will confirm eligibility and obtain written informed consent. Once consent has been obtained baseline tests will be completed.

1.10. Proposed Recruitment and schedule (updated 14 June 2012,)



Predicted recruitment was originally based on randomisation of 10-11 patients per month, this has been revised and the predicted (new) randomisation rate is 6 patients per month.

2. Randomisation

Eligible patients who fulfil the inclusion/exclusion criteria and have provided full written consent after they have had sufficient time for discussion and consideration, will be randomised (in a 1:1 ratio) to receive either their routine AVR using a full median sternotomy approach or AVR using upper limited sternotomy performed in J-shape into the right 4th intercostal space.

Patient allocations will be computer generated by the trial statistician and will be in random permuted blocks of variable lengths, stratified by surgeon and by type of valve (bioprosthetic or mechanical).

On the day of their cardiac surgery, a member of the surgical team/research nurse will register the participating patient with the R&D unit by telephone. Patient details, surgeon and planned AVR procedure will be recorded by R&D personnel who are not otherwise directly involved with the trial. Once this registration is complete the group allocation will be released to the surgical team and perfusionists.

It will not be possible to blind patients or the surgical and clinical team to the surgical approach used for the study. However the outcomes of 'fitness for discharge', pain, wound infection and health related quality of life will be collected by trained research staff, not involved in routine care, using standardised protocols.

3. Procedure

3.1. Mini-sternotomy procedure

The patient is positioned supine in the operating table with a sandbag between the scapulae. The skin incision is made starting half way down the manubrium downwards for 8 cm. Skin flap is then raised upwards and the sternum exposed till the 4th intercostal space. The manubrium is divided in the midline using a vertical saw from the manubrium downward and then into the right 4th intercostal space. The thymus is then divided in the midline and pericardium opened exposing the ascending aorta, aortic root, right atrial appendage and the right ventricular infundibulum.

3.2. Procedures are common to both trial groups

The patient is fully heparinised with standard dose of heparin. The aorta is then cannulated using a wired flexible aortic cannula of suitable size. The right atrial appendage is cannulated using a flat venous cannula and cardiopulmonary bypass is instituted. The cardioplegia cannula and right superior pulmonary vein vent is inserted as standard, aorta cross-clamped and cardioplegia administered. The aorta is then incised open in an oblique or transverse fashion, the diseased valve excised and annulus decalcified. An aortic valve prosthesis of suitable make (tissue or mechanical) and size is then inserted. The aortotomy is then closed, heart de-aired and patient weaned off cardiopulmonary bypass in standard fashion. Drains are inserted into the mediastinum and right pleura and pacing wires to the right atrium and ventricle.

3.3. Conversion from mini-sternotomy to full-sternotomy

Conversion to full-sternotomy will be done without hesitation if, after opening the pericardium, access to the aortic root proves difficult (~5% of cases). All patients will have a transoesophageal echocardiogram in theatre at conclusion of the operation, before the chest is closed to confirm perfect valve implantation and function of the prosthesis.

4. Patient follow up

4.1. Follow up visits and Travel expenses (see also section 1.5)

Patients will be assessed by our research nurse daily while in hospital to assess pain; drug use; wound status; bleeding; level of mobilisation and respiratory function. Following discharge patients will be assessed after 6 weeks at a routine clinic appointment, at 6 months during a research visit to the hospital and at 12 months using postal questionnaires or telephone interviews. Patient travel expenses, including parking charges will be reimbursed for the six month research visit.

4.2. Adverse Events and Serious Adverse Events

4.2.1. Defining Adverse Events

Adverse Event (AE)

The definition of an adverse event is: 'Any untoward medical occurrence in a patient which does not necessarily have a causal relationship with this treatment'. This includes 'any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the study treatment'. This may include, for example, a cold or an accident.

Serious Adverse Event (SAE)

The definition of a serious adverse event is one that fulfils at least one of the following criteria:

- Is fatal- results in death
- Is life threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Medically significant or requires intervention to prevent at least one of the outcomes listed above

SUSAR

The definition of a suspected unexpected serious adverse reaction (SUSAR) is a serious adverse event that is thought to be possibly or definitely related to the study treatment.

Expected adverse events

Expected adverse events following AVR surgery (using either surgical approach) will include but are not limited to abnormal mental status, atrial fibrillation, atrial flutter, other cardiac arrhythmias, aortic dissection, bleeding events surgical or non-surgical, cardiac arrest; cardiac failure, cardiac surgical complications; cardiac tamponade; death, endocarditis, invasive line infections, hospital acquired infections, neurological event (and consequences) exacerbation of existing/concomitant conditions, gastro-intestinal complications, haemothorax, , multi-organ failure, myocardial ischaemia/infarction, pericardial effusion, perivalvular leak, pleural effusion, pneumothorax, pulmonary oedema, renal compromise or failure, respiratory compromise or failure, respiratory infection, sepsis, thrombo-embolic event, sternotomy wound infection.

Recording Adverse events

All events meeting the definition of an adverse event will be collected and reported from the start of surgery until hospital discharge. All SAEs will be recorded until the subject has completed the trial.

- Documenting of adverse events is the responsibility of the Principle Investigator and Clinical Research Nurse
- Standard documentation for reporting AEs for MiniStern at Papworth will be available in the trial site file
- At each visit or study assessment, adverse events that have occurred since the previous visit will be elicited from the patient. The event will be detailed in the patient's notes, as source document verification, including the start date (if known) and the end date.
- Any treatment/medication given for the event, including the dates the treatment/medication was commenced and the date it was stopped/changed will be documented.
- All research staff in contact with patients are responsible for noting adverse events that are reported by the patient and making them known to the Principle Investigator and Clinical Research Nurse
- Events that are ongoing at the final study visit will be followed up as clinically indicated.

4.2.2. Reporting Adverse events

- All serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) will be documented as above using the appropriate reporting documentation and must be reported to the Sponsor within 24 hours of the Chief Investigator/Clinical Research Nurse being aware.
- SUSARs must be reported to the Sponsor within 24 hours of the Chief Investigator/Clinical Research Nurse being aware.
- SUSAR reports will be submitted to the REC by the sponsor within 14 days
- Expected SAEs will be reported to the LREC in the annual REC report
- Completed SAE forms will be stored with the patient's study documentation. A photocopy should also be filed in the investigator site file.

5. Data Collection and auditing

5.1. Case Report Form Completion

The clinical research nurse will record all trial data on a series of pre-prepared case report forms (CRFs). These forms will be returned to Papworth R&D unit. The R&D unit will be responsible for data monitoring and quality control. A data quality and scanning officer will check the HRQoL data for missing values and prepare this data for analysis.

5.2. Source Documentation

The investigator/clinical research nurse will maintain source documents (patient's hospital case notes) for each patient in the study. A copy of the consent form and patient information sheet will be filed in the patient's case notes. All information in the CRFs, apart from the questionnaires, must be traceable to and consistent with the source documents in the patient's hospital case notes (Ref. ICH/GCP 4.9.2).

5.3. Errors and Corrections

Any change or correction to CRF should be dated, initialled, and explained (if necessary) and should not obscure the original entry.

5.4. Storage of Documents

CRFs will be kept in a locked filing cabinet or a locked room.

5.5. Monitoring and Audit

The project data will monitored by R&D Unit personnel independent of the trial. The first two patients will be monitored in full. Thereafter, one patient a month will be monitored up to a total of 10% of study patients, for consent, inclusion and exclusion criteria, adverse event reporting and primary outcome data.

6. Data Analysis

6.1. Statistical Analysis

All statistical analyses and reporting will comply with CONSORT guidelines [14] where possible. For all outcomes all patients will be included in the analysis in the group to which they were randomised (ITT). Initial length of stay will be compared using the Student-T test since, although hospital stay is not normally distributed, the Central Limit Theorem suggests that means will have approximately Normal distribution, provided the sample is large. Time to all cause death will be explored using Kaplan- Meier curves. Pain, health related quality of life scores and the EQ-5D utility score will be compared using Likelihood Ratio Tests from linear regression models including baseline levels and treatment group. Repeated measures and time ordering will be modelled appropriately. For patients who die or are lost to follow up multiple imputation methods will be used based on regression predictions. Details of these analyses will be finalised when the pattern and amount of missing data is known.

6.2. Economic Analysis

An NHS perspective will be adopted for the economic analysis. The analysis will be consistent with the NICE reference case (Methodology Guidelines 2008 [15]). For both groups patient-specific resource use data will be collected until all patients have completed 12-months post-randomisation.

The average cost of initial cardiac surgery will be based on the capital cost of equipment, variable costs, staff and overhead costs. Staff and overhead costs will be allocated according to theatre time and annual patient throughput. Variable consumable costs (e.g. blood products, IV heparin) will also be recorded prospectively on a per patient basis.

Resource use will be monitored from surgery to 36 months post-randomisation and information collected on readmissions to hospital, further cardiac procedures, GP and outpatient visits and cardiac-related medication. Patients will be asked to record medications taken, inpatient and outpatient visits and any procedures on a standard questionnaire to be administered with the EQ-5D. Patient responses will be validated against hospital and primary care records. Unit costs will be taken from the hospital accounting system for each participating centre and nationally published estimates [16, 17].

At baseline, day 4, on discharge, 6 weeks, and 6 monthly thereafter (maximum 36 months) post surgery all patients will be asked to complete the EuroQoL questionnaire. The social tariff for the EQ-5D, as estimated by Dolan et al will be applied to each patient's self-reported classification in order to calculate utility values [13]. Using actual rather than nominal times of assessment and assuming a linear change in values between time points, patient-specific utility curves up to 12-months post randomisation will be calculated. A value of zero will be applied at the date of death for those patients who died.

The QALYs experienced by each patient to 12-months post randomisation will be calculated as the area under their utility curve to 12-months or time of death, whichever occurs first. In order to adjust for differences in baseline utilities a linear regression will be fitted to the utilities post treatment, with baseline utility and treatment group as explanatory variables. Treatment effects will be taken from the treatment group coefficient of this regression. For patients who do not complete all EuroQoL/resource use measurements and are censored, the methods of Willan and Lin [18] will be used to estimate mean QALYs and costs. The incremental cost-effectiveness ratio (ICER), calculated as the ratio of the difference in costs and QALYs, will be estimated using the sample means. In order to generate confidence intervals without assuming any parametric form for the distribution of the costs, bootstrapping will be used to resample patients and repeat the calculations described above at least 1000 times [19]. Measurements will be summarised as the mean and 95% confidence interval, estimated using bootstrapping. The bootstrap samples for the treatment comparison will also be plotted on the cost-effectiveness plane. In addition, cost-effectiveness acceptability curves (CEAC) for these comparisons will be plotted. The CEAC plots the probability that a procedure is cost-effective for differing values of a QALY. Sensitivity analysis will be used to explore the impact of the deterministic variables within the economic analysis (e.g. unit cost estimates and discount rate).

7. Management & Governance

Overall project management will be taken on by Papworth R&D Unit who will also assume Sponsorship responsibilities of behalf of Papworth Hospital NHS Foundation Trust. The R&D Unit has an established track record of managing clinical trials including several national multi-centre surgical RCTs.

A Trial Management Protocol, based on the R&D Unit's standard template, will be used to guide and inform management of the trial. The trial will be conducted to the highest standards and will be compliant with all Statutory and Regulatory requirements including the Research Governance Framework and GCP. A signed delegation log will clarify individual responsibilities.

The Trial Manager will assume day-to-day responsibility for the trial. They will meet at least monthly with the Chief Investigator and also with the Senior R&D Manager and weekly with the Trial Nurse. These meetings will review progress against timelines, troubleshoot, review financial matters and ensure timely reporting to internal (R&D Committee) and external (e.g. West Anglia CLRN) groups.

R&D Unit personnel independent of the trial will undertake monitoring and audit as described in section 6.5.

An independently chaired Trial Steering Group will meet at least six monthly and an independent Data Monitoring and Ethics Committee will meet annually. Both will have patient representatives.

7.1. Trial Steering Group (TSG)

The TSG will monitor the progress of the trial in relation to the stated milestones and the interim and overall objectives and instigate any remedial actions. It will also review any relevant information from other sources and implement recommendations from the Data Monitoring and Ethics Committee (DMEC). The TSG will be responsible for reports to the NIHR, REC and WACLRN.

7.2. Data Monitoring and Ethics Committee (DMEC)

A separate Data Monitoring and Ethics Committee (DMEC) will also be convened as nominated by the TSG at their first meeting. The DMEC will meet annually but will be in regular contact to view the data and the results of any interim analysis and to instruct un-blinding if necessary. The DMEC membership will include a clinician, a statistician and a health economist independent of the TSC, the study and the Chief Investigator.

8. References

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2. Sackett DL, Haynes RB, Tugwell P. Clinical epidemiology: a basic science for clinical medicine. Boston, MA: Little Brown, 1985.
3. Bonacchi M, Prifti E, Giunti G, Frati G, Sani G. Does ministernotomy improve postoperative outcome in aortic valve operation? A prospective randomized study. Ann Thorac Surg 2002; 73(2):460-5; discussion 465-6.
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Annex 1

Discharge protocol for patient after aortic valve replacement:

After aortic valve replacement, generally patients are considered fit to be discharged once they satisfy the following criteria:

Pacing wires are removed.
Dependable cardiac rhythm is present.
Drains are removed and acceptable post-drain removal chest x-ray.
Patient's body weight is back to preoperative body weight or below.
Patient mobilises well and ambulates without assistance. The patient should be able to walk (with mobility aid if required but unassisted) 80 metres on the flat and up and down a flight of stairs if they have stairs at home.
Anticoagulation clinic arrangements are made in the local hospital.
Occupational therapy and Physiotherapy clearance obtained.

Social factors like lack of help at home, domestic and financial issues, delays in arranging hospital transport, delays in inter-hospital transfer, delay organising occupational health personnel visits to assess patient's residence etc might contribute to delays in hospital discharge. Hence, we have decided to have the day of "fit to be discharged" as treatment time in hospital for patients included in this trial.

Annex 2 Visual and numerical analogue pain score

Annex 3 CROQ-AVR questionnaires

Annex 4 Health Protection Agency Protocol for the Surveillance of Surgical Site Infection version 4, July 2008

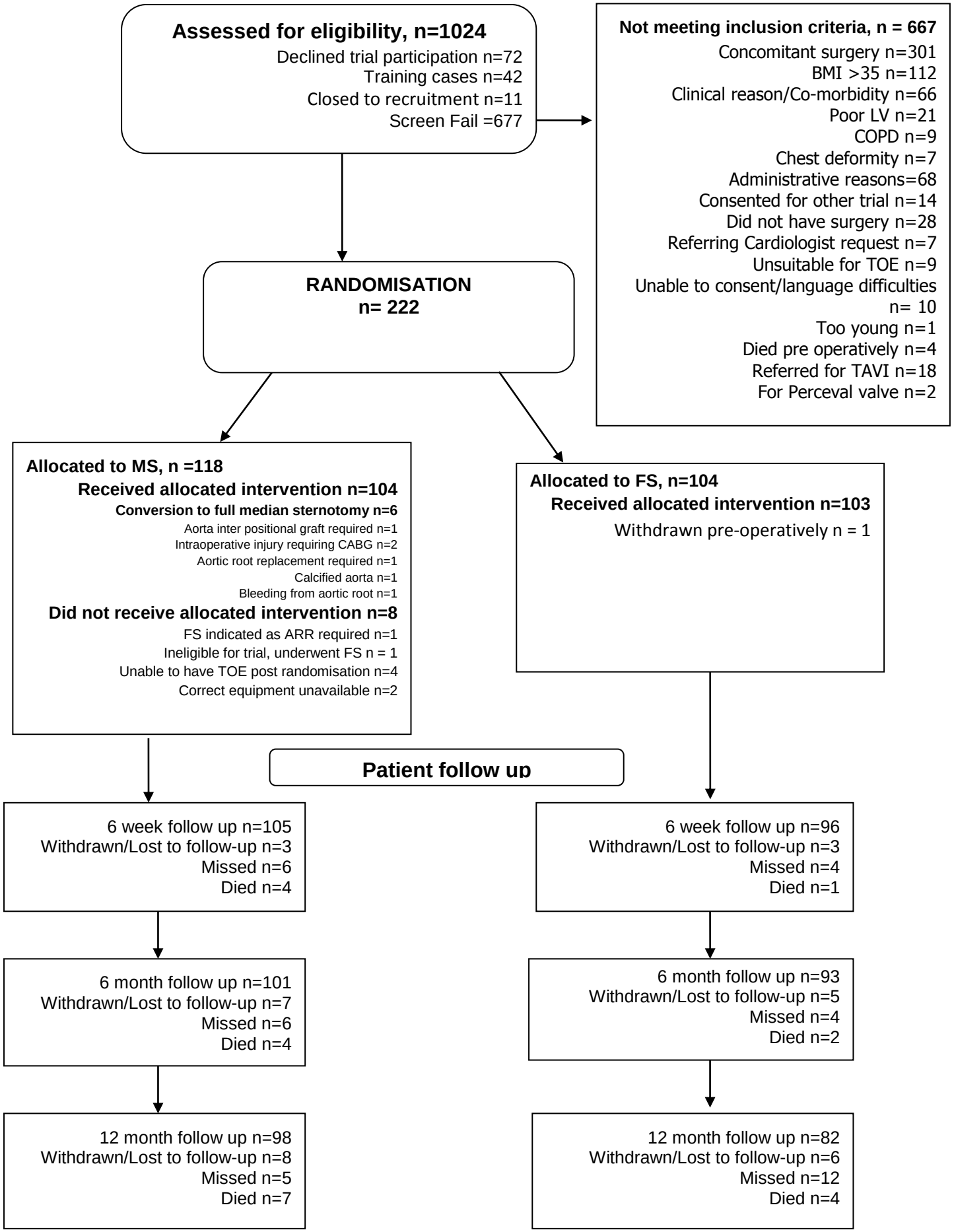
CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	6
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	7-9
	2b	Specific objectives or hypotheses	8
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	8
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	8
	4b	Settings and locations where the data were collected	8-9
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	10-11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	9-10
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines	13
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	9
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	9
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	9
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	9

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	NA
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	12-13
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	12-13
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	14 and Fig 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	14 and Fig 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	14
	14b	Why the trial ended or was stopped	14
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	14, 12
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	14-16 and figures
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	14-16
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	appendix
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	15,16 and appendix
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	18-19
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	18-19
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	16-18
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	Online
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	1

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

MiniStern Trial. CONSORT Flow Diagram



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PATIENT INFORMATION SHEET

PART 1

1. Study title: The MiniStern Trial – A Pragmatic, Prospective, Randomised, Controlled Trial Comparing Upper Mini Sternotomy to Full Median Sternotomy as a Surgical Approach for Aortic Valve Replacement

Chief Investigator: Mr Sukumaran Nair, Consultant Cardiothoracic surgeon

2. Invitation paragraph

We would like to invite you to take part in a research study called the MiniStern Trial.

Before you decide you need to understand why the research is being done and what it will involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish.

Please ask if there is anything that is not clear or you would like more information. Further information can be obtained from the Therapeutics & Cardiac Research Team, Freeman Hospital, Newcastle upon Tyne, NE7 7DN. Tel: 0191 2137201.

3. What is the purpose of the study?

Aortic valve replacement (AVR) is an operation used to relieve the symptoms of a narrowed or leaky heart valve and reduce the risk of future heart failure. Patients may have symptoms such as shortness of breath, chest pain, dizziness or fainting spells. AVR is the second most common open heart operation in the UK and increasing numbers of patients are referred for AVR each year.

During an AVR operation the chest is cut open via the breastbone (or sternum); this incision is called a sternotomy. A heart bypass machine is used to keep the blood circulating while the heart is stopped for surgery. The surgeon then opens the aorta (the big artery coming out of the heart) takes out the old valve and stitches in the new one. The aorta is closed, the heart is restarted, the bypass machine is stopped and the sternotomy wound is closed.

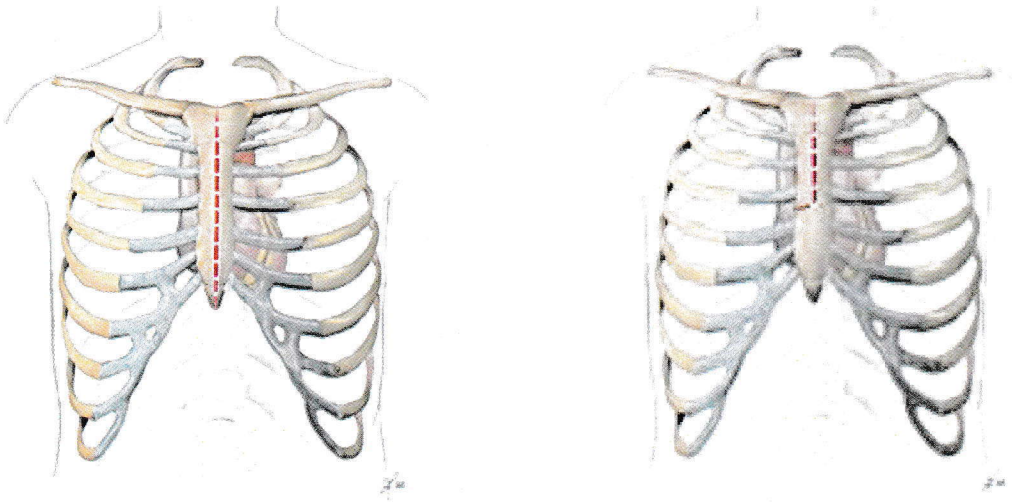
The aim of this study is to compare two different techniques for opening the chest for AVR. We would like to find out if there is any difference in the length of time patients stay in hospital after each of these techniques and also to find out if a smaller incision can help to speed up recovery after the operation but maintain the overall success of the surgery.

4. What are the techniques being compared?

Conventional AVR surgery requires the surgeon to open the chest wall via an incision all the way from the collar bone to the bottom of the breast bone; this is called a *full median*

sternotomy. More recently a technique called *mini-sternotomy* has been used, which involves making a much shorter incision in the chest.

Full Median Sternotomy *Mini-sternotomy*



A few research studies have already compared mini-sternotomy to full median sternotomy for AVR but they have only studied small numbers of patients and none of the studies were carried out in the UK. These studies suggest that mini-sternotomy AVR may be associated with less post operative pain, less blood loss, fewer lung and wound complications and a shorter length of hospital stay than full sternotomy. However, they also suggest that the operation may take longer, and for about 1 in 20 patients it will be necessary to open the chest wall further to complete the operation successfully.

At present, surgeons in the UK offer the mini sternotomy procedure to some patients but not others. Some patients accept it and others do not. Neither the surgeons nor the patients truly know if mini sternotomy can help to reduce hospital stay or improve recovery after an AVR operation. This study is designed to answer this important question.

The MiniStern trial will compare patients having an AVR operation with a full median sternotomy to those having an AVR operation using mini-sternotomy. To make it fair, the two groups must be similar. We can achieve this by putting patients in one or another group at random. This is like tossing a coin and is done by a computer. This type of study is called a randomised study. If you take part in the MiniStern trial you will have a 1 in 2 chance (fifty-fifty) of getting the mini or the median sternotomy procedure.

5. Why have I been invited?

Your surgeon has identified you as someone who is going to have their first AVR at the Freeman Hospital.

6. Do I have to take part?

No. It is entirely up to you to decide if you want to take part.

Your surgeon will have spoken to you about the study when you came to clinic and will have given you this information sheet to take home. You can then discuss the study with your GP, relatives and friends. A member of the research team will call you at home to see if you are interested in taking part and to talk about the study in more detail, answering any questions you may have.

About 2-4 weeks before your AVR surgery you will attend a routine pre-admission clinic at the hospital. This will again give you the chance to ask for more information from your surgeon and research nurse or coordinator.

If you do not want to take part you will have your AVR as planned, using full median sternotomy, and will continue to be looked after by your surgeons in exactly the same way.

If you are happy to participate you will be asked to sign the consent form that is attached to this information sheet.

You are free to withdraw at any time without giving a reason. This will not affect the standard of care that you receive.

7. What will happen to me if I take part?

At Pre-admission clinic: Our research nurse will ask you to perform some simple breathing tests and to complete some standard quality of life questionnaires. These will as far as possible be incorporated into your normal schedule of activities for the visit and will add no longer than an hour to the visit. These procedures will be repeated again at regular intervals after your surgery.

Before your operation: When you come in for your operation, our research nurse will visit you and ask you to confirm that you are still willing to participate in this study. The nurse will then check with you if there have been any changes to your health and well being since you were assessed at the pre-admission clinic.

On the day of your surgery, the surgical team performing your operation will contact the Research Unit at Papworth hospital to find out whether you have been randomised to mini or full sternotomy and your operation will continue using the appropriate technique.

After your operation: When you wake up your wound will be covered by a dressing but you will be able to find out which technique you were allocated to by asking your nurse or surgeon.

You will be given pain relief medication which will be delivered by a continuous drip into your vein (this is routine practice after all AVR operations). When you are awake and able your nurses will teach you to use a special PCA (patient controlled analgesia) pump so that you can control delivery of pain medication as you require. PCA pumps would normally be used after mini-sternotomy but for this study they will also be provided after full sternotomy. When you no longer require the PCA pump you will be given Paracetamol tablets as required.

The research nurse will visit you, as far as possible each day, to assess your pain and to make a record of the pain medication you are taking. She will also look at your wound and collect data about this too.

On day of discharge from hospital: You will have had a routine transthoracic echocardiogram or 'Echo' before your operation. This is performed on the surface of your chest and is like an ultrasound. The Echo assesses the functioning of your aortic and other valves and strength and capability of your pumping chambers in your heart. This will be repeated prior to your discharge from hospital. You will also be asked to repeat the simple breathing test and a one page quality of life questionnaire.

6-8 weeks after your operation: The 6-week visit is a routine hospital visit. In addition to your routine follow up you will be asked to repeat the breathing test and the quality of life questionnaires. The research nurse will also ask you how you are feeling and if you have had any side effects from the operation. She will assess your pain levels, your wound healing and any medications you have been taking.

6 months after your operation: At 6 months after the operation we will ask you to come to the hospital again for an extra research visit. At that visit the research nurse will see you to perform the breathing/lung function test, assess your general health and well being, checking for any side effects, and will also have arranged for you to have another 'Echo' to assess your heart and new valve function. She will also give you the questionnaires about your quality of life and patient satisfaction to complete. We will pay your travel expenses, including parking charges for this extra research visit.

After 12 months the research nurse or a member of the team will be in touch by telephone to discuss your health and how you have been feeling or if you have had any side effects. She will also either post the quality of life questionnaires or work through them with you over the telephone, depending on what you would prefer. After this, the research team will contact you by telephone or post every six months, for up to 3 years to find out how you are getting on.

The findings of the study will be regularly monitored as the study proceeds. If at any time we find that one group is doing significantly better than the other, we will have answered the question and the study will be stopped.

8. What are the possible disadvantages and risks of taking part?

The mini-sternotomy is not a new procedure and the surgeons involved in this study are all experienced in conducting AVR surgery.

Performing a mini-sternotomy may lengthen your operation by about 30 minutes, because access to the heart is slightly more difficult. There is no evidence that the risks from the operation will be increased because the operation takes longer.

There is a potential risk with mini sternotomy AVR of not being able to access the heart as well as can be achieved with full median sternotomy. However conversion to full median sternotomy will be done without hesitation if access proves difficult.

The additional research visit at 6 months may be inconvenient. You will be reimbursed for travel and parking costs associated with this additional visit..

9. What are the possible benefits of taking part?

Your surgeon cannot guarantee that you will receive any personal benefit from participating in this study. The benefits that you experience will depend on the results of the study and the group that you are allocated to. If the study shows that patients' hospital stay and quality of life are improved by mini-sternotomy and you are randomised to this group then you may benefit.

If you participate in this study you will have the advantage that your health will be monitored more closely than patients who do not take part in the study. You will also be contributing to the information we can give future patients having AVR operations.

10. What will happen to me when the research study stops?

Your doctors will continue to monitor your health according to routine practice.

11. What if something goes wrong?

Any complaint about the way you have been treated during the study or any possible harm you might suffer will be addressed. Further detailed information is included in Part 2.

12. Will my taking part in this study be kept confidential?

Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

13. Contact details:

If you have any questions about this study please contact:-

Mrs Lesley Bremner
Research Nurse
Therapeutics & Cardiac Research Team

Lesley.Bremner@nuth.nhs.uk
Tel: 0191 2137201

Mr Sukumaran Nair
Consultant Cardiothoracic Surgeon and
Chief Investigator

Sukumaran.Nair@nuth.nhs.uk
Tel: 0191 2137702

Thank you for taking the time to read this.

This completes Part 1 of the Information Sheet.

If the information in Part 1 has interested you and you are considering participating please read the additional information in Part 2 before making a decision.

PART 2

1. What if relevant new information becomes available?

The study will be overseen by an independent Committee. Its role is to check that the study is run correctly and to ensure that patients remain safe.

If this Committee or the research surgeons hear of relevant new information during the course of this study, they will tell you about it and discuss whether you should continue in the study.

If the study is stopped for any reason we will tell you and arrange for your care to continue.

2. What will happen if I don't want to carry on with the study?

If you wish us to stop collecting your medical information then we will do so. However we will need to use the information collected up until the time that you decided to withdraw from the study.

3. What if there is a problem?

If you are concerned about any aspect of this study you should ask to speak to one of the researchers who will do their best to answer your questions (contact details at the end of this Information Sheet). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure.

If something goes wrong and you are harmed during the study due to someone's negligence then you may have grounds for a legal action for compensation against the hospital involved, but you may have to pay your legal costs. The normal NHS complaints mechanisms will still be available to you.

NHS hospitals are unable to agree in advance to pay compensation for non-negligent harm (situations where no one can be blamed for what happened). However, NHS Trusts are able to consider offering an ex-gratia payment in the case of a claim.

4. Will my taking part in this study be kept confidential?

All information that is collected about you during the course of this study will be kept strictly confidential according to the Data Protection Act 1998. It will be placed in a study file and given a study number so that you cannot be identified personally. This anonymous information will be used by members of the research team.

If you join the study you also agree that certain members of the study team and representatives of regulatory authorities can have access to your medical records (ie information that will identify you personally). This will be necessary for your surgeon to manage your treatment and for the study team and authorities to check that the study is being carried out correctly. Your personal information is routinely registered on national databases and we will ask you to agree that researchers can have access to this information so that they can keep in contact with you during the study.

All the people involved in this study have a duty of confidentiality to you as a research participant and will ensure that nothing that could reveal your identity will be disclosed outside the research site.

Information on paper will be kept in locked filing cabinets and where possible behind security coded, locked doors. Electronic information will be kept on computers that are protected by passwords. Any information about you that leaves the hospital will be anonymous and anything that could identify you (name, date of birth, address, hospital number) will be removed and you will only be identified by a study code. When the study is reported to the funding agency, published in medical journals or presented at conferences it will not be possible to identify you personally.

With your consent, we will inform your GP that you are participating in this study.

5. What will happen to the results of the research study?

The results of the study will be published in medical journals, presented at national and international medical conferences and described in reports submitted to the funding agency and regulatory authorities. You will not be named or identified in any report of the study. You may receive copies of these publications if you wish to.

6. Who is organising and funding the research?

The research is organised by Papworth Hospital and funded by the Research for Patient Benefit Programme of the National Institute for Health Research. Your surgeon will not be paid for including you in this study.

7. Who has reviewed the study?

The study was reviewed by the Research for Patient Benefit Programme reviewers and has been given a favourable ethical opinion by Essex Research Ethics Committee.

Thank you for considering taking part in this study.

If you decide to participate you will be asked to sign a consent form and will be given a copy of this information sheet and the consent form to keep.

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

The Freeman Hospital
High Heaton
Newcastle upon Tyne
NE7 7DN

Tel: 0191 233 6161
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Patient Identification Number:

CONSENT FORM

Study title: The MiniStern Trial – A Pragmatic, Prospective, Randomised, Controlled Trial Comparing Upper Mini Sternotomy to Full Median Sternotomy as a Surgical Approach for Aortic Valve Replacement

Chief Investigator: Mr Sukumaran Nair

Please initial box

1. I confirm that I have read and understood the information sheet dated 29 October 2013 (version 5) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of my medical notes and information collected during the study may be looked at by responsible individuals from regulatory authorities or from the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
4. I agree that researchers can have access to information about me that is registered on national databases. ☐
5. I consent to my GP being informed of my participation in this study. ☐
6. I agree to take part in the above study. ☐

Name of Patient	Date	Signature
Name of person taking consent	Date	Signature

When completed, 1 for patient; 1 for researcher site file (original); 1 to be kept with hospital notes